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Appendices only

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A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis

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Appendix 1

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

An estimate of the fracture risk for women with average BMD and no prior fracture was calculated assuming that there are only three sets of patient type at each age: patients with a *T*-score of –2.5 SD or lower and with a prior fracture (group A), patients with a *T*-score of –2.5 SD or lower and without a prior fracture (group B), and those patients with an average BMD and without prior fracture (group C). The incidence rate in group C is the answer that was required to estimate the risks for patients with different BMD and fracture status.

For this calculation it was assumed that a prior fracture will increase the risk of subsequent fractures (at all sites) by two-fold compared with group C. The increased risk due to a woman being osteoporotic was calculated from the data in *Tables 2* and *3* of the main report (see Chapter 2). An example of calculating the relative risks in groups A and B for hip fracture is provided for women aged 70 years.

For group B, where patients have a *T*-score of –2.5 SD, the *Z*-score will equal –0.81. This will equate to an increased risk of hip fracture of $2.78^{0.81}$, which is 2.29.

For group A, where patients have a *T*-score of –2.5 SD and have suffered a prior fracture, the increased risk is assumed to be $2.29 \times 2 = 4.58$.

The relative risks of groups A and B, by age and fracture site, are given in *Table 128*.

Given the simplifying assumptions, the risk of fracture for group C can be calculated once estimates of the percentage of patients suffering osteoporosis and severe osteoporosis are found. Data on the percentage of patients osteoporotic (including severe) were taken from Holt and Khaw,[10] using the femoral neck as the measurement site.

Data from Kanis and colleagues[13] indicate that the percentages of all fractures that are first fractures are approximately 90% below the age of 70 years, and 80% above 70 years. Assuming these figures to be applicable in the UK, then using the overall incidence of fracture since the age of 45 years and adjusting for mortality rates it is estimated that the percentages of the population with severe osteoporosis are as given in *Table 129* (calculations not shown). It is assumed that all fractures at the hip, spine, wrist or proximal humerus were caused by osteoporosis.

The example of calculating the risk of hip fracture for the groups at the age of 70 years will be continued.

TABLE 128 *Relative risk of fracture for women with a* T*-score of –2.5 SD, with or without a prior fracture*

	Hip		Vertebral		Wrist		Proximal humerus	
Age (years)	**Group A**	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
50	21.99	10.99	5.90	2.95	3.71	1.86	4.75	2.37
55	13.51	6.75	5.06	2.53	3.40	1.70	4.20	2.10
60	8.89	4.45	4.37	2.19	3.13	1.56	3.74	1.87
65	6.23	3.11	3.75	1.88	2.87	1.43	3.31	1.65
70	4.58	2.29	3.22	1.61	2.63	1.31	2.93	1.46
75	3.40	1.70	2.78	1.39	2.41	1.21	2.60	1.30
80	2.56	1.28	2.39	1.19	2.21	1.11	2.30	1.15
85	2.07	1.03	2.06	1.03	2.03	1.02	2.05	1.02

TABLE 129 *Assumed proportion of women with severe osteoporosis, by age*

Age (years)	Population of women with severe osteoporosis
50	2%
55	3%
60	6%
65	9%
70	14%
75	21%
80	28%

At 70 years of age it is expected that 55% of the population would be in group C. Of the remaining patients 14% are expected to suffer from severe osteoporosis (group A) and thus 31% suffer from osteoporosis (group B).

The average incidence of hip fracture at 70 years of age is estimated to be 0.49%, from Singer and colleagues.[12]

This will be comprised of:

(Percentage in group A × RR group A × Group C risk) + (Percentage in group B × RR group B × Group C risk) + (Percentage in group C × Group C risk)

= (14% × 4.58 × Group C risk) + (31% × 2.29 × Group C risk) + (55% × Group C risk)

= 190% × Group C risk

Since this equals the average incidence of 0.49%, the risk in group C must equal 0.49%/1.90 = 0.26%.

This methodology was repeated for all fracture sites and all ages. The estimated incidences of fractures by age band are given in *Table 4* of the main report (see Chapter 2). Sensitivity analyses were conducted which showed that the average risk of a healthy woman did not change markedly with small changes in the percentages of patients with severe osteoporosis.

Appendix 2

Electronic bibliographic databases searched

1 BIOSIS previews
2 CCTR (Cochrane Controlled Trials Register)
3 CDSR (Cochrane Database of Systematic Reviews)
4 CINAHL
5 EBM Reviews – ACP Journal Club
6 EMBASE
7 HEED (Health Economic Evaluations Database)
8 MEDLINE
9 NHS DARE (Database of Assessments of Reviews of Effectiveness)
10 NHS EED (Economic Evaluations Database)
11 NHS HTA (Health Technology Assessment)
12 PreMEDLINE
13 Science Citation Index
14 Social Sciences Citation Index

Appendix 3

Other sources searched

1 AHRQ (Agency for Healthcare Research and Quality), USA
2 Bandolier
3 British Geriatrics Society – Gastro Special Interests Group
4 British Oncological Association
5 CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
6 CenterWatch
7 CHE (Centre for Health Economics), York
8 Clinical Evidence
9 CliniWeb
10 COIN (Department of Health)
11 CriB (Current Research in Britain)
12 DES Reports (West Midlands Health Technology Assessment Collaboration)
13 Department of Health
14 eBNF (electronic British National Formulary)
15 eGuidelines
16 Health Evidence Bulletin, Wales
17 HSRU (Health Services Research Unit), Aberdeen
18 INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
19 MRC (Medical Research Centre) Trials Register
20 National Osteoporosis Society
21 National Osteoporosis Foundation, USA
22 National Guidelines Clearinghouse
23 NCCHTA (National Coordinating Centre for Health Technology Assessment)
24 POINT (Department of Health)
25 Royal College of General Practitioners
26 Royal College of Nursing
27 Royal College of Physicians
28 Royal College of Radiologists
29 Royal College of Surgeons
30 Royal Pharmaceutical Society
31 ScHARR (School of Health and Related Research, University of Sheffield) Library catalogue
32 SIGN (Scottish Intercollegiate Guidelines Network)
33 Trent Working Group on Acute Purchasing Reports
34 Wessex DEC (Development and Evaluation Committee) Reports
35 WHO

Appendix 4

MEDLINE search strategies used

Osteoporosis search (MEDLINE *1966–2002: Ovid Biomed*) *Search undertaken May and September 2002*

#1 Exp osteoporosis/
#2 Osteoporo$.tw
#3 Bone diseases, metabolic/
#4 or/1-3
#5 (Bone adj6 densit$).tw
#6 Bone density/
#7 (Bone or bones).mp
#8 Exp densitometry/
#9 Tomography, x-ray computed/
#10 Densit$.tw
#11 9 and 10
#12 8 or 11
#13 7 and 12
#14 5 or 6 or 13
#15 Colles' fracture/
#16 Exp hip fractures/
#17 Spinal fractures/
#18 15 or 16 or 17
#19 Fractures/
#20 Colles$.tw
#21 (Hip or hips).tw
#22 (Femur adj6 neck).tw
#23 (Femoral adj6 neck).tw
#24 (Spine or spinal).tw
#25 Vertebra$.tw
#26 Lumbar vertebrae/
#27 Or/20-26
#28 19 and 27
#29 Fractur$.tw
#30 ((Fractur$ adj6 colles$) or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$).tw
#31 29 or 30
#32 14 or 18 or 28 or 31
#33 4 and 32

Breast cancer utilities search (MEDLINE *1992–2002: Ovid Biomed*) *Search undertaken October 2002*

#1 Exp *breast neoplasms/
#2 Exp *CARCINOMA/
#3 Breast$.tw
#4 2 and 3
#5 ((Breast$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or metasta$ or carcinoma$)).ti
#6 1 or 4 or 5
#7 Exp *Quality-Adjusted Life Years/
#8 Health state value$.tw
#9 Health state utilit$ value$.tw
#10 Quality adjusted life year$.tw
#11 (Euroqol or eq5d or eq 5d).tw
#12 QALY$.tw
#13 Health utilit$.tw
#14 HUI.tw
#15 Quality of well being.tw
#16 Quality of wellbeing$.tw
#17 QWB.tw
#18 (QALD$ or QALE$ or QTIME).tw
#19 or/7-18
#20 6 and 19

Osteoporosis fractures utilities (MEDLINE *1992–2002: Ovid Biomed*) *Search undertaken November 2002*

#1 Colles' fracture/
#2 Exp hip fractures/
#3 Spinal fractures
#4 Or/1-3
#5 Fractures/
#6 Colles$.tw
#7 (Hip or hips).tw
#8 (Femur adj6 neck).tw
#9 (Femoral adj6 neck).tw
#10 (Spine or spinal).tw
#11 Vertebra$.tw
#12 Lumbar vertebrae/
#13 Or/6-12
#14 5 and 13
#15 Fractur$.tw
#16 ((Fractur$ adj6 colles$) or (hip or hips) or (femur adj6 neck) or (femoral adj6 neck) or (spine or spinal) or vertebra$).tw
#17 15 or 16
#18 4 or 14 or 17
#19 Exp osteoporosis/
#20 Osteoporo$.tw
#21 Bone diseases, metabolic/

#22 Or/19-21
#23 18 and 22
#24 Exp *Quality-Adjusted Life Years/
#25 Health state value$.tw
#26 Health state utilit$ value$.tw
#27 Quality adjusted life year$.tw
#28 (Euroqol or eq5d or eq 5d).tw
#29 QALY$.tw
#30 Health utilit$.tw
#31 HUI.tw
#32 Quality of well being.tw
#33 Quality of wellbeing$.tw
#34 QWB.tw
#35 (QALD$ or QALE$ or QTIME).tw
#36 Or/24-35
#37 23 and 36

Appendix 5

Methodological search filters used in OVID MEDLINE

Systematic reviews/meta-analyses

#1. Meta-analysis/
#2. Exp review literature/
#3. (Meta-analy$ or meta analy$ or metaanaly$).tw
#4. Meta analysis.pt
#5. Review academic.pt
#6. Review literature.pt
#7. Letter.pt
#8. Review of reported cases.pt
#9. Historical article.pt
#10. Review multicase.pt
#11. or/1-6
#12. or/7-10
#13. 11 not 12

Randomised controlled trials

#1. Randomized controlled trial.pt
#2. Controlled clinical trial.pt
#3. Randomized controlled trials/
#4. Random allocation/
#5. Double blind method/
#6. Single blind method/
#7. or/1-6
#8. Clinical trial.pt
#9. Exp clinical trials/
#10. ((Clin$) adj25 (trial$)).ti,ab
#11. ((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
#12. Placebos/
#13. Placebos.ti,ab
#14. Random.ti,ab
#15. Research design/
#16. or/8-15
#17. Comparative study/
#18. Exp evaluation studies/
#19. Follow up studies/
#20. (Control$ or prospectiv$ or volunteer$).ti,ab
#21. Prospective studies/
#22. or/17-21
#23. 7 or 16 or 22

Economic and quality of life evaluations

#1. Economics/
#2. Exp "costs and cost analysis"/
#3. Economic value of life/
#4. Exp economics, hospital/
#5. Exp economics, medical/
#6. Economics, nursing/
#7. Economics, pharmaceutical/
#8. Exp models, economic/
#9. Exp "fees and charges"/
#10. Exp budgets/
#11. Ec.fs.
#12. (Cost or costs or costed or costly or costing$).tw
#13. (Economic$ or pharmacoeconomic$ or price$ or pricing).tw
#14. Quality-adjusted life years/
#15. "Economic burden".tw
#16. Cost of illness/
#17. Exp quality of life/
#18. Quality of life.tw
#19. Life quality.tw
#20. Hql.tw
#21. Sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
#22. Qol.tw
#23. (Euroqol or eq5d or eq 5d).tw
#24. Qaly$.tw
#25. Quality adjusted life year$.tw
#26. Hye$.tw
#27. Health$ year$ equivalent$.tw
#28. Health utilit$.tw
#29. HUI.tw
#30. Quality of wellbeing$.tw
#31. Qwb.tw
#32. Quality of well being.tw
#33. (Qald$ or qale$ or qtime$).tw
#34. or/1-33

Appendix 6

Quality assessment tool

TABLE 130 *Quality assessment tool*

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

Appendix 7

Studies with fracture as a primary end-point, by intervention

- Alendronate: Fracture Intervention Trial fracture and non-fracture arms[98,99]
- Etidronate: Storm *et al.*, 1990;[123] Watts *et al.*, 1990[124]
- Risedronate: Harris *et al.*, 1999;[132] McClung *et al.*, 2001;[134] Reginster *et al.*, 2000[135]
- Raloxifene: MORE study, 1999[138]
- Teriparatide: Neer *et al.*, 2001[151]
- Calcium: Orimo *et al.*, 1987;[158] Recker *et al.*, 1996;[159] Tilyard *et al.*, 1992[160]
- Calcium plus vitamin D: Chapuy *et al.*, 1994;[165] Chapuy *et al.*, 2002[166]
- Calcitriol: Gallagher *et al.*, 1989;[87] Tilyard *et al.*, 1992[160]
- Oestrogen: Mosekilde *et al.*, 2000[179]

Appendix 8

Trials meeting the inclusion criteria for review

* Indicates the major publication for the study.

Adami, 1995

Adami S, Baroni MC, Broggini M, Carratelli L, Caruso I, Gnessi L, *et al*. Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. *Osteoporos Int* 1993;**3** (Suppl 3):S21–7.

*Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, *et al*. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;**17**:383–90.

Aitken, 1973

*Aitken JM, Hart DM, Lindsay R. Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. *BMJ* 1973;**3**:515–18.

Alendronate Osteoporosis Prevention Study (AOPS)

*McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, *et al*. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Ann Intern Med* 1998;**128**:253–61.

Alexandersen, 1999

*Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. *J Clin Endocrinol Metab* 1999;**84**:3013–20.

Aloia, 1988

*Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. *Am J Med* 1988;**84**:401–8.

Arthur, 1990

*Arthur RS, Piraino B, Candib D, Cooperstein L, Chen T, West C, Puschett J. Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. *Mineral and Electrolyte Metabolism* 1990;**16**:385–90.

Baeksgaard, 1998

*Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int* 1998;**8**:255–60.

Bjarnason, 2000

*Bjarnason NH, Christiansen C. Early response in biochemical markers predicts long-term response in bone mass during hormone replacement therapy in early postmenopausal women. *Bone* 2000;**26**:561–9.

Body, 2001

*Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, *et al*. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;**87**:4528–35.

Body JJ, Gaich GA, Scheele WH, Miller PD, Kulkarni PM, Hodsman AB. A randomized controlled clinical trial to compare the efficacy of LY333334 [recombinant human parathyroid hormone (1–34)] and alendronate sodium in postmenopausal women with osteoporosis. *J Bone Miner Res* 2001;**16**:S179.

Bone, 1997

*Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein R, Licata AA, *et al*. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. *J Clin Endocrinol Metab* 1997;**82**:265–74.

Weinstein RS, Bone H, Tucci J, Downs R, Harris S, Licata A, *et al*. Alendronate treatment of osteoporosis in elderly women. *J Bone Miner Res* 1994;**9**(Suppl 1): S144.

Bone, 2000

*Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, *et al*. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab* 2000;**85**:720–6.

Bravo, 1996

*Bravo G, Gauthier P, Roy PM, Payette H, Gaulin P, Harvey M, *et al*. Impact of a 12-month exercise program on the physical and psychological health of osteopenic women. *J Am Geriatr Soc* 1996; **44**:756–62.

Caniggia, 1984

*Caniggia A, Delling G, Nuti R, Lore F, Vattimo A. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D_3, estradiol and placebo in post-menopausal osteoporosis. *Acta Vitaminologica et Enzymologica* 1984;**6**:117–28.

Carfora, 1998
*Carfora E, Sergio F, Bellini P, Sergio C, Falco D, Zarcone R. Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. *Gazzetta Medica Italiana – Archivio per le Scienze Mediche* 1998; **157**:105–9.

Cauley, 2001
*Cauley JA, Black DM, Barrett-Connor E, Harris F, Shields K, Applegate W, *et al*. Effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med* 2001;**110**:442–50.

Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials* 1998; **19**:314–35.

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280**:605–13.

Chapuy, 1994
*Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994;**308**:1081–82.

Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, *et al*. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;**327**:1637–42.

Chapuy MC, Arlot M, Duboeuf F, Meunier PJ. Prevention of non vertebral fractures and cortical bone loss in elderly women: a prospective controlled trial using calcium and vitamin D_3 supplements. *Osteoporos Int* 1993;**3** (Suppl 1);258.

Chapuy MC, Meunier PJ. Prevention of secondary hyperparathyroidism and hip fracture in elderly women with calcium and vitamin D_3 supplements. *Osteoporos Int* 1996;**6**(Suppl 3):S60–3.

Chapuy, 2002
*Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, *et al*. Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the decalyos II study. *Osteoporos Int* 2002;**13**:257–64.

Cheng, 2000
*Cheng S, Sipila S, Puolakka H, Suominen H. Effects of hormone replacement therapy and high impact physical activity on bone/muscle ratio in postmenopausal women. *Osteoporos Int* 2000;**11**:175.

Chesnut, 1995
*Chesnut CH III, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, *et al*. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995;**99**:144–52.

Clemmesen, 1997
*Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int* 1997; **7**:488–95.

Cosman, 2001
*Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, *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**:925–31.

Lindsay R, Cosman F, Nieves J, Dempster DW, Shen V. A controlled clinical trial of the effects of 1-34Hpth in estrogen-treated osteoporotic women. *J Bone Miner Res* 1993;**8**:S130.

Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, *et al*. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;**350**:550–5.

Delmas, 2000
*Delmas PD, Confavreux E, Garnero P, Fardellone P, de Vernejoul MC, Cormier C, *et al*. A combination of low doses of 17 beta-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. *Osteoporos Int* 2000;**11**:177–87.

Dursun, 2001
*Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. *Int J Clin Pract* 2001; **55**:505–9.

Ebrahim, 1997
*Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* 1997;**26**:253–60.

Thompson PW, Baskaran V, Evans K, Ebrahim S. Randomized controlled trial of brisk walking in the prevention of osteoporosis. *Osteoporos Int* 1996; **6**(Suppl 1):237.

Eiken, 1997
*Eiken P, Pors NS, Kolthoff N. Effects on bone mass after eight years of hormonal replacement therapy. *British Journal of Obstetrics and Gynaecology*. 1997; **104**:702–7.

EPIC study
Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, *et al*. Prevention of bone loss with alendronate in postmenopausal women under

60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;**338**:485–92.

*Ravn P, Bidstrup M, Wasnich RD, Davis JW, McClung MR, Balske A, *et al*. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. *Ann Intern Med* 1999; **131**:935–42.

Falch, 1987

Falch JA, Odegaard OR, Finnanger AM. 3 years treatment with $1,25(OH)_2$ vitamin D_3 does not reduce bone loss or fracture rate in postmenopausal women with fracture of the distal forearm. In Norman AW, Schaefer K, Grigoleit H, van Herrath D, editors. *Vitamin D. Chemical, biochemical and clinical update*. Berlin: Walter de Gruyter; 1985. pp. 1004–5.

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*Winegard K, Papaioannou A, Parkinson W, Ferko N, Adachi JD, McCartney M. Twelve month efficacy of home-based exercise for improving the quality of life of elderly women with symptomatic osteoporosis related vertebral fractures. *J Bone Miner Res* 2001; **16**:S409.

WHI trial
*Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.

Zarcone, 1997
*Zarcone R, Carfora E, Sergio F, Bellini P, Longo M, Tartaglia E, Tomasillo G. Estrogeno-terapia in donne con osteoporosi post-menopausale [Oestrogen therapy in women with postmenopausal osteoporosis]. *Minerva Ginecol* 1997;**49**:355–9.

Appendix 9

Studies excluded from the review of clinical effectiveness

TABLE 131 *Studies excluded from clinical effectiveness review*

Study	Reason for exclusion
Bassey EJ. Exercise for prevention of osteoporotic fracture. *Age Ageing* 2001;**30** (Suppl 30):31.	Unavailable within the study timescale
Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, *et al*. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int* 1994;**4**:245–52.	Subjects include men
Dilsen G, Gülbaba G, Sindel D. Calcitriol in the treatment of osteoporosis. *Osteoporos Int* 1998;**8**(Suppl 3):101.	Does not provide results relating to the control arm
Ettinger B, Black DM, Mitlak BH, Rosenfeld JA, *et al*. Can the prophylactic use of raloxifene, a selective estrogen-receptor modulator, prevent bone mineral loss and fractures in women with diagnosed osteoporosis or vertebral fractures? *Western Journal of Medicine* 2000;**173**:173–88.	Unavailable within the study timescale
Fukunaga M, Kushida K, Kishimoto H, Shiraki M, Taketani Y, Minaguchi H, *et al*. A comparison of the effect of risedronate and etidronate on lumber bone mineral density in Japanese patients with involutional osteoporosis: a randomized controlled trial. *Osteoporos Int* 2002;**13**:S31.	Subjects include two men (Fukunaga M: personal communication)
Kiel DP. Preventing nonvertebral fractures with vitamin D-3 and calcium. *Ann Intern Med* 1993;**118**(Suppl 3):66.	Unavailable within the study timescale
Leoliger EA, Harris ST. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis. *American Journal of Medicine* 1995;**99**:225.	Letter
Lufkin EG, Wahner HW, O'Fallon WM, Kiel DP. Transdermal estrogen for postmenopausal osteoporosis. *Ann Intern Med* 2001;**118**(Suppl 1):8.	Unavailable within the study timescale
Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JA. Can vitamin D supplementation reduce the risk of fracture in the elderly? *J Bone Miner Res* 2002;**17**:709–15.	Subjects include men
Mosekilde L, Beck-Nielsen H, Sorensen OH, Nielsen SP, Charles P, Vestergaard P, *et al*. Hormone replacement therapy reduces the risk of forearm fracture in postmenopausal women. Results of the Danish Osteoporosis Prevention Study. *Ugeskr Laeger* 2001;**163**:7064–9	From the abstract, it is clear that it reports the same study and results as Mosekilde *et al*., 2000[179]
Reeve J, Mitchell A, Tellez M, Hulme P, Green JR, Wardley-Smith B, Mitchell R. Treatment with parathyroid peptides and estrogen replacement for severe postmenopausal vertebral osteoporosis: prediction of long-term responses in spine and femur. *J Bone Miner Metab* 2001;**19**:102–14	Not truly randomised
Roux C, Keller M, Eastell R, McKeever C, Pack S, Ethgen D, *et al*. Risedronate significantly reduces vertebral and non-vertebral fractures in osteoporotic women. *J Bone Miner Res* 1999;**14** (Suppl 1):S538.	Pools data from two (unspecified) RCTs
Shintani M, Beppu KI, Hara Y. Effect of etidronate therapy on lumbar spine bone mineral density in women with osteopenia or osteoporosis. *Acta Obstet Gynaecol Jpn* 1998;**50**:186–8.	It was not possible to obtain a translation of this Japanese paper within the study timescale
Sinaki M, Mikkelsen BA. Postmenopausal spinal osteoporosis: flexion versus extension exercises. *Arch Phys Med Rehabil* 1984;**65**:593–6.	Subjects not randomised to treatment groups

continued

TABLE 131 *Studies excluded from clinical effectiveness review (cont'd)*

Study	Reason for exclusion
Sorensen OH, Kollerup G, Storm T, Thamsborg G, Jorgensen NR, Genant HK. Effect of long-term etidronate treatment on bone mass and spinal fracture rate. *Osteoporos Int* 1996;**6**(Suppl 1):267.	Not an RCT
Storm T, Thamsborg G, Sorensen HA, Kollerup G, Genant HK, Sorensen OH. Long-term treatment with intermittent cyclical etidronate: effect on bone mass and fracture rate. *J Bone Miner Res* 1992;**7**(Suppl 1):S117.	Not an RCT
Storm T, Kollerup G, Thamsborg G, Genant HK, Sorensen OH. Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis. *J Rheumatol* 1996;**23**:1560–64.	Not an RCT

Appendix 10

Details of included studies

TABLE 132 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Adami, 1995[93]	Italy	2 years	BMD (spine)	Postmenopausal women with osteoporosis or osteopenia (lumbar *T*-score ⩽–2), 5% of whom had vertebral fracture at entry	59 (48–76)	Rx1: 10 mg per day oral alendronate Rx2: 20 mg per day oral alendronate Rx3: 100 IU per day intranasal salmon calcitonin All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Body, 2002[94]	Multi-national	Median 14 months	Change in lumbar spine BMD	Postmenopausal women with osteoporosis (spine or hip *T*-score <–2.5)	66 (30–85)	Alendronate sodium (10 mg per day) + 1000 mg per day calcium and 400–1200 IU per day vitamin D	Once-daily subcutaneous teriparatide (40 μg per day) + 1000 mg per day calcium and 400–1200 IU per day vitamin D
Bone, 1997[95]	USA	2 years	Lumbar BMD	Postmenopausal women with osteopenia or osteoporosis (*T*-score <–2, but no more than one lumbar crush fracture), 37% of whom had vertebral fracture at entry	70.7 (60–85)	Rx1: 1.0 mg per day oral alendronate Rx2: 2.5 mg per day oral alendronate Rx3: 5.0 mg per day oral alendronate All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Bone, 2000[52]	USA	2 years	Lumbar BMD	Hysterectomised postmenopausal women with lumbar spine BMD <0.862 g cm^{-2} (Hologic) (mean *T*-score –2.5 ± 0.2)	61.4	Rx1: 10 mg per day oral alendronate Rx2: 0.625 mg per day CEE Rx3: 10 mg per day oral alendronate plus 0.625 mg per day CEE All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Carfora, 1998[96]	Italy	30 months	BMD,[a] vertebral fractures;[a] biochemical markers[a]	Postmenopausal women with osteoporosis (lumbar spine *T*-score <–2.5)	(44–73)	Rx1: 5 mgper day oral alendronate Rx2: 10 mg per day oral alendronate Rx3: 20 mg per day oral alendronate for 15 months, placebo for 15 months All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium

continued

TABLE 132 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Chesnut, 1995[54]	USA	2 years	Lumbar BMD	Postmenopausal women with osteopenia (lumbar spine BMD $\leq$0.88 g cm^{-2}), but no vertebral or hip fractures attributable to osteoporosis	63 (42–75)	Rx1: 5 mg per day oral alendronate Rx2: 10 mg per day oral alendronate Rx3: 20 mg per day oral alendronate for 1 year, placebo for 1 year Rx4: 40 mg per day oral alendronate for 1 year, placebo for 1 year Rx5: 40 mg per day oral alendronate for 3 months, 2.5 mg per day for 21 months All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Dursun, 2001[97]	Turkey	1 year	Lumbar and hip BMD	Postmenopausal women with osteoporosis or osteopenia (lumbar spine *T*-score $\leq$–2 SD)	61.2	Rx1: 10 mg per day oral alendronate Rx2: 100 IU per day intranasal salmon calcitonin All subjects received 1000 mg per day calcium	1000 mg per day calcium
FIT: women with pre-existing fractures[98]	USA	Mean 2.9 years	Proportion of women with new vertebral fractures	Postmenopausal women with severe osteoporosis (at least one existing vertebral fracture)	70.8 (55–81)	5 mg per day oral alendronate increased at 24 months to 10 mg per day	Placebo
FIT: women without pre-existing fractures[99]	USA	Mean 4.2 years	Proportion of women with incident non-pathological, non-traumatic clinical fractures (non-vertebral and symptomatic vertebral fractures)	Postmenopausal women with osteoporosis or osteopenia (femoral neck BMD 0.68 g cm^{-2}), but no vertebral fractures	67.7 (54–81)	5 mg per day oral alendronate increased at 24 months to 10 mg per day	Placebo

continued

TABLE 132 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Greenspan, 2002[60]	USA	2 years	BMD	Elderly women living in residential care with osteoporosis or osteopenia (lumbar or total hip BMD <–2)	78.5 (65–91)	10 mg per day oral alendronate + 400 IU per day vitamin D	Placebo + 400 IU per day vitamin D
Liberman, 1995[100]	Multi-national	3 years	Effect on BMD at lumbar spine; safety and tolerability of daily oral alendronate; effect on calcium-regulating hormones; effect on biochemical indices of bone turnover	Postmenopausal women with osteoporosis (lumbar *T*-score <–2.5), but no vertebral fractures	64 (45–80)	Rx1: 1.5 mg per day oral alendronate Rx2: 10 mg per day oral alendronate Rx3: 20 mg per day oral alendronate years 1–2, 5 mg per day year 3 All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Lindsay, 1999[101]	USA	1 year	Lumbar BMD	Postmenopausal women with osteoporosis or osteopenia already receiving HRT (*T*-score at lumbar spine or femoral neck <–2 and at the other site <1.5), 57% of whom had a previous fracture	61.7 (⩾40)	10 mg per day oral alendronate + 400 IU per day vitamin D	Placebo and 400 IU vitamin D
Pols, 1999[102]	Multi-national	1 year	Lumbar BMD	Postmenopausal women with osteoporosis or osteopenia (lumbar *T*-score <–2)	62.8 (39–84)	10 mg per day oral alendronate + 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Rossini, 1994[103]	Italy	18 months	BMD	Postmenopausal women with osteoporosis or osteopenia (spinal BMD >2 SD below adult mean without vertebral fractures)	62.5 (59–69)	20 mg per day oral alendronate followed by 12 months of calcium-controlled diet	Placebo followed by 12 months of calcium-controlled diet

[a] Does not differentiate between primary and secondary outcome measures.
Rx, treatment.

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Adami, 1995[93]	⩾2 years past natural menopause, lumbar spine *T*-score ⩽–2 (<0.99 g cm^{-2} for Lunar densitometers, and <0.86 g cm^{-2} for Hologic, Norland and Sophos)	Evidence of any secondary cause of osteoporosis, other metabolic bone disease, hyperthyroidism or hypothyroidism, or any associated health problems that could affect their participation in the study or interfere with the interpretation of the data; having received calcitonin, oestrogen, progestogen, anabolic steroids, glucocorticoids, or high doses of vitamin D or vitamin A for >2 weeks in the 6 months before baseline; ever having been treated with fluoride in doses >1 mg per day or with any bisphosphonate	Generally comparable. However, the percentage of regular cigarette smokers was substantially lower in the placebo group than in the treatment groups (9.9% vs 19.1% in the 10 mg group, 15.3 in the 20 mg group and 17.3 in the calcitonin group)	NA: only clinically apparent fractures were recorded	A placebo of alendronate was used, but no placebo was available for the intranasal calcitonin. Thus, it is not certain that assessors of fracture outcomes were blinded to treatment allocation
Body, 2002[94]	Ambulatory women at least 5 years postmenopause and aged 30–85 years, with no severe or chronically disabling conditions other than osteoporosis, and with lumbar spine or femoral neck *T*-score ⩽–2.5	Metabolic bone disorders; diseases affecting bone and mineral metabolism; carcinoma within the previous 5 years; nephrolithiasis or urolithiasis within the previous 2 years; malabsorption; significantly impaired renal or hepatic function; abnormalities of the lumbar spine prohibiting assessment of BMD at L2–L4; medications or drugs known to affect bone or mineral metabolism (e.g. androgens, anabolic steroids, bisphosphonates, calcitonin, glucocorticoids, oestrogens, fluoride) in the prior 2–24 months (depending on the drug); alcohol abuse; allergy or previous exposure to teriparatide, exogenous PTH or PTH analogues	Comparable	NA	The study, planned to last for 2 years, was voluntarily brought to an early closure after a median of 14 months to evaluate the clinical relevance in humans of the observation of osteosarcoma made in Fischer 344 rats in a carcinogenicity study of teriparatide

continued

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Bone, 1997[95]	Women aged 60–85 years, in generally good health, with lumbar spine BMD $\leq$0.944 g cm^{-2} for Lunar densitometers, $\leq$0.824 g cm^{-2} for Hologic	More than one lumbar spinal crush fracture, or spinal anatomy otherwise unsuitable for DXA analysis; a history of recent major GI disease (e.g. peptic ulcer, oesophageal disorder or malabsorption) or having recently used a drug to inhibit gastric acid secretion for >2 weeks; receiving chronic NSAID therapy or agents known to affect bone metabolism (e.g. etidronate, calcitonin, oestrogen, glucocorticoids or fluoride). Patients receiving thyroid hormone replacement were required to have been on a stable dose for $\geq$6 months before study entry, and to be euthyroid; clinically significant vitamin D deficiency was similarly excluded or corrected	Comparable	A decrease of $\geq$20% in vertebral height (method described by Genant, 1993)[225]	–
Bone, 2000[52]	Prior hysterectomy (to avoid any possible confounding effects of progestin therapy or withdrawal bleeding); lumbar spine BMD <0.862 g cm^{-2} as measured by Hologic densitometry equipment for at least three evaluable vertebrae in the L1–L4 region	Evidence of metabolic bone disease other than postmenopausal osteoporosis; low serum 25-hydroxyvitamin D concentration (<10 ng ml^{-1}); concomitant therapy with drugs that affect bone turnover (including bisphosphonates, calcitonin, fluoride); renal insufficiency; severe cardiac disease; history of recent major upper GI mucosal erosive disease (including significant upper GI bleeding, recurrent peptic ulcer disease, and oesophageal or gastric varices); any underlying condition that would contraindicate randomisation to oestrogen; having taken any form of systemic HRT in the 6 months preceding study entry	Comparable	Only clinical fractures were reported, as adverse events	Mean *T*-score at baseline approximately –2.5

continued

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Carfora, 1998[96]	Postmenopausal for 5 years, with osteoporosis (lumbar spine *T*-score ⩽–2.5)	Other causes of osteoporosis (treatment with glucocorticoids); other disorders of bone and mineral metabolism (vitamin D deficiency, Paget's disease, hyperparathyroidism); active peptic ulcer disease; abnormal renal function; abnormal hepatic function; abnormalities of the lumbar spine	Comparable	Definition not given	–
Chesnut, 1995[54]	Healthy women aged 42–75 years; postmenopausal for ⩾5 years; lumbar spine BMD ⩽0.88 g cm^{-2} (*T*-score approximately –2)	Any disease or drug therapy potentially affecting bone metabolism; presence of spine or hip fractures attributable to osteoporosis	The placebo and pooled treatment groups were comparable at baseline, except that the treatment group had a lower serum osteocalcin level	Definition not given	–
Dursun, 2001[97]	*T*-score ⩽–2 at either the posteroanterior lumbar spine or the femoral neck	Documented history of drug or alcohol abuse; evidence of any bone metabolism disorder; active GI or liver disease; renal failure; renal calculi; treatment with specific therapy for osteoporosis; systemic corticosteroid therapy; malignancy; disorder of calcium metabolism; lumbar vertebrae abnormalities preventing the evaluation of BMD	Comparable, except that the alendronate group had an energy level score lower than that of the calcitonin group, and an emotional reaction score lower than the calcitonin and control groups, on the NHP	A decrease of 20% and ⩾4 mm in any vertebral height between baseline and end of study	Differences between the groups at baseline in terms of energy level and emotional reaction may have affected the reliability of the results in relation to those parameters of quality of life
FIT: women with pre-existing fractures[98]	Postmenopausal for ⩾2 years; femoral neck BMD ⩽0.68 g cm^{-2} and at least one vertebral fracture	Peptic ulcer disease; dyspepsia requiring daily treatment; abnormal renal function; major medical problems that would be likely to preclude participation for 3 years; severe malabsorption syndrome; uncontrolled hypertension; MI during the previous 6 months; unstable angina; evidence of disturbed thyroid or parathyroid function; having taken oestrogen or calcitonin within the previous 6 months or bisphosphonates or sodium fluoride (>1 mg day for ⩾2 weeks) at any time	Comparable	A decrease of ⩾20% in anterior, middle or posterior height between baseline and end of study. In addition, for any vertebra that was deformed at baseline, an absolute change of ⩾4 mm	–

continued

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
FIT: women without pre-existing fractures[99]	Postmenopausal for ⩾2 years; femoral neck BMD ⩽0.68 g cm^{-2}	Peptic ulcer disease; dyspepsia requiring daily treatment; significant renal or hepatic dysfunction; major medical problems that would be likely to preclude participation for 3 years; severe malabsorption syndrome; uncontrolled hypertension; MI during the previous 6 months; unstable angina; hypothyroidism, hyperthyroidism or hyperparathyroidism; having taken oestrogen or calcitonin within the previous 6 months or bisphosphonates or sodium fluoride (>1 mg per day for ⩾2 weeks) at any time; vertebral fracture	Comparable	A decrease of 20% in anterior, middle or posterior height between baseline and end of study. In addition, for any vertebra that was deformed at baseline, an absolute change of ⩾4 mm	Although women who had taken oestrogen in the preceding 6 months were excluded from the study, 9.2% of women in the treatment group and 11.1% in the placebo group took oestrogen at some time during the study; this would tend to reduce the difference between the treatment and placebo groups
Greenspan, 2002[60]	Aged ⩾65 years; ambulatory but living in long-term residential care (not facilities that housed independent, community-dwelling, elderly people); with osteoporosis or osteopenia (lumbar or total hip BMD <–2)	Disorders of bone mineralisation; 25-hydroxycholecalciferol level <25 nmol l^{-1}; untreated hyperthyroidism; recent major upper GI mucosal erosive disease; use of bone-active agents	The treatment groups were said to be comparable at baseline, but no further information was given (not even the number of women in each group)	NA	–
Liberman, 1995[100]	Postmenopausal for ⩾5 years, with osteoporosis (defined as *T*-score at lumbar spine ⩽–2.5)	Other causes of osteoporosis (e.g. treatment with glucocorticoids); other disorders of bone and mineral metabolism (e.g. vitamin D deficiency, Paget's disease, hyperparathyroidism); active peptic ulcer disease; abnormal renal function; abnormalities of the lumbar spine precluding assessment of BMD at a minimum of three lumbar vertebrae; history of hip fracture; any prior treatment with bisphosphonates or treatment within the previous 12 months with oestrogen, progestin, calcitonin, fluoride or anabolic steroids	Baseline characteristics were only given for the 881 women who were included in the analysis of vertebral fractures, and there is no information regarding the comparability of all groups at entry	A reduction of ⩾20%, with an absolute decrease of ⩾4 mm, in the height of any vertebral body between baseline and follow-up	Pools the results of two very similar trials. This pooling was planned from the outset as it was anticipated that the numbers would otherwise not be large enough to allow the detection of a significant effect

continued

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lindsay, 1999[101]	⩾40 years of age (⩾25 years if surgically menopausal); postmenopausal for ⩾5 years; receiving ongoing HRT (approximately equivalent to ⩾0.625 mg per day of CEE) for ⩾1 year before study entry; *T*-score ⩽–2 at lumbar spine or femoral neck, and ⩽1.5 at the other site	Contraindications to HRT; treatment with any agent other than HRT that might influence bone turnover; untreated hyperthyroidism; disorders of bone mineralisation; conditions that affect oesophageal emptying; dosages of any drug that might alter calcium metabolism	Comparable	Symptomatic fractures only	Randomisation was stratified according to duration of previous HRT to ensure the equal distribution between the groups of women who had received HRT for less or more than 2 years. The mean duration of HRT use was approximately 10 years
Pols, 1999[102]	Postmenopausal for ⩾3 years; age ⩽85 years; lumbar spine *T*-score ⩽–2; in good health and between 20% below and 50% above ideal body weight; at least three vertebrae from L1–L4 evaluable by DXA	Metabolic bone disease other than postmenopausal osteoporosis; disturbed thyroid or parathyroid function; major GI disease (e.g. peptic ulcer or malabsorption) in previous year; use of a drug to inhibit gastric acid secretion for >2 weeks within 3 months of study entry; MI in previous year; uncontrolled hypertension or untreated angina; significantly impaired renal function; evidence of significant end-organ disease; having received a bisphosphonate or fluoride (>8 mg per day) during the previous 6 months, or oestrogen (except for vaginal ⩽3 times per week), ipriflavone or calcitonin during the previous 4 months, or any anabolic steroid, glucocorticoid or progestin for ⩾2 weeks during the previous 6 months; receiving any medication that might alter bone or mineral metabolism (including vitamin A >10,000 IU per day, vitamin D >1000 IU per day, anticonvulsants or phosphate-binding antacids)	Comparable	Non-vertebral fractures only	–

continued

TABLE 133 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Rossini, 1994[103]	⩾5 years past natural menopause; lumbar spine *T*-score ⩽–2	Affected by disorders known to influence bone mass; treated with oestrogens or other drugs interfering with bone or mineral metabolism for any significant length of time in the past year	Comparable	Not stated	–

TABLE 134 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Adami, 1995[93]	2	3	3	3	1	0	12/15 (80)	Rx1: 68 Rx2: 72 Rx3: 75 C: 71	86% overall	Not specified
Body, 2002[94]	1	1	3	3	3	0	11/15 (73)	Rx1: 73 Rx2: 73	Rx1: 78% Rx2: 70%	Pharmaceutical companies
Bone, 1997[95]	2	3	3	3	3	3	17/18 (94)	Rx1: 86 Rx2: 89 Rx3.93 C: 91	Rx1: 58% Rx2: 67% Rx3: 67% C: 61%	Pharmaceutical company
Bone, 2000[52]	3	1	3	3	1	0	11/15 (73)	Rx1: 92 Rx 2: 143 Rx 3: 140 C: 50	Rx1: 74% Rx2: 76% Rx3: 79% C: 68%	Pharmaceutical company
Carfora, 1998[96]	1	1	1	3	0	1	7/15 (47)	Rx1: 34 Rx2: 34 Rx3: 34 C: 34	Not specified	Not specified

continued

TABLE 134 *Studies of alendronate in women with postmenopausal osteoporosis or osteopenia: methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Chesnut, 1995[54]	2	3	3	2	1	1	12/18 (67)	Rx1: 32 Rx2: 30 Rx3: 32 Rx4: 32 Rx5: 31 C: 31	82% overall	Pharmaceutical company
Dursun, 2001[97]	1	1	1	2	0	3	8/15 (53)	Rx1: 51 Rx2: 50 C: 50	Not specified	Not specified
FIT: women with pre-existing fractures[98]	3	3	3	3	3	3	18/18 (100)	Rx: 1022 C: 1005	Not specified	Pharmaceutical
FIT: women without pre-existing fractures[99]	3	3	3	3	3	3	18/18 (100)	Rx: 2214 C: 2218	Not specified	Pharmaceutical company
Greenspan, 2002[60]	3	3	3	3	1	0	13/15 (87)	327 overall	Not specified	Pharmaceutical company
Liberman, 1995[100]	2	3	3	1	1	3	13/18 (72)	Rx1: 202 Rx2: 196 Rx3: 199 C: 397	Rx: 84% C: 84%	Pharmaceutical company
Lindsay, 1999[101]	2	3	3	3	1	1	13/18 (72)	Rx: 214 C: 214	Rx: 95% C: 89%	Pharmaceutical company
Pols, 1999[102]	2	3	3	3	3	0	14/15 (93)	Rx: 950 C: 958	Rx: 88% C: 90%	Pharmaceutical company
Rossini, 1994[103]	1	1	3	3	0	1	9/15 (60)	Rx: 15 C: 15	Rx: 100% C: 100%	Not specified

C, control.

TABLE 135 *Studies of alendronate in postmenopausal women with normal BMD or osteopenia*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
AOPS[66]	Multinational	3 years	BMD	Healthy, recently postmenopausal, women without osteoporosis	51.8 (40–59)	Rx1: 1 mg per day oral alendronate Rx2: 5 mg per day oral alendronate Rx3: 10 mg per day oral alendronate Rx4: 20 mg per day oral alendronate years 1–2, placebo year 3	Placebo
EPIC study[71]	USA, Europe	6 years	BMD	Healthy postmenopausal women no more than 10% of whom had a lumbar spine BMD below 0.8 g cm^{-2}	53.3 (45–59)	Rx1: 2.5 mg per day oral alendronate for 6 years Rx2: 2.5 mg per day oral alendronate for 4 years followed by placebo for 2 years Rx3: 2.5 mg per day oral alendronate for 2 years followed by placebo for 2 years Rx4: 5 mg per day oral alendronate for 6 years Rx5: 5 mg per day oral alendronate for 4 years followed by placebo for 2 years Rx6: 5 mg per day oral alendronate for 2 years followed by placebo for 4 years Rx7: open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22, and 1 mg per day estradiol on days 23–28) for 4 years Rx8: placebo for 4 years followed by 5 mg per day oral alendronate for 2 years	Placebo

TABLE 136 *Studies of alendronate in women with normal BMD or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
AOPS[66]	Healthy women aged 40–59 years who had experienced menopause 6–36 months before enrolment	Spinal BMD more than 2 SD above or below normal peak BMD; history of non-traumatic spine or hip fracture; disorders of bone and mineral metabolism; major upper GI diseases (e.g. peptic ulcer, oesophageal disease, malabsorption) within the previous year; previous treatment with bisphosphonates or fluoride (>1 mg per day); treatment in previous 12 months with oestrogen, progestin, calcitonin, glucocorticoids, anticonvulsant agents, phosphate-binding antacids, or excessive vitamin A or vitamin D; regular use (>4 times per week) of any medication with the potential to cause GI irritation (e.g. aspirin); smoking more than 20 cigarettes per day; drinking ⩾3 alcoholic beverages per day	Comparable	Not given	–
EPIC study[71]	Postmenopausal for ⩾6 months; in good health, with no clinical or laboratory evidence of systemic disease	Abnormal renal function; history of cancer, peptic ulcer or oesophageal disease requiring prescription medication within the previous 5 years; previous treatment with a bisphosphonate or with fluoride; regular treatment with a phosphate-binding antacid; oestrogen-replacement therapy within the previous 3 months; therapy with any other drug that affects the skeleton. Only 10% of women enrolled at each centre were allowed to have a lumbar spine BMD <0.8 g cm^{-2}	Comparable	NA; only symptomatic fractures recorded	NA; only clinical fractures were reported

TABLE 137 *Studies of alendronate in women with normal BMD or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
AOPS[66]	2	3	1	3	0	0	9/12 (75)	Rx1: 92 Rx2: 88 Rx3: 88 Rx4: 89 C: 90	70% overall	Pharmaceutical company
EPIC study[71]	2	3	3	3	1	0	12/15 (75)	Rx1: 165 Rx2: 165 Rx3: 169 Rx4: 168 Rx5: 165 Rx6: 165 Rx7: 110 Rx8: 250 C: 252	Rx1: 50% Rx2: 58% Rx3: 77%[a] Rx4: 54% Rx5: 52% Rx6: 57% Rx7: 25%[a] Rx8: 47% C: 52%	Pharmaceutical company

[a] At 4 years.

TABLE 138 *Alendronate: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Adami, 1995[93]	13% of women taking alendronate and 14% of the placebo group had at least one upper GI adverse event. There was only one case of gastritis, in the placebo group; no oesophagitis or gastro-oesophageal mucosal erosion were reported	All treatment groups were similar to placebo	Alendronate 10 mg: 3% Alendronate 20 mg: 8% Placebo: 6%
AOPS[66]	Clinically significant upper GI adverse events were seen in 26% of the 1 and 5 mg groups, 30% of the 10 mg group, 32% of the 290 mg group and 29% of the placebo group. Of these, only flatulence and odynophagia showed dose-related increases	Clinical adverse events (including mild common symptoms such as headache and upper respiratory infection) occurred in more than 90% of each group	Alendronate 1 mg: 7% Alendronate 5 mg: 7% Alendronate 10 mg: 7% Alendronate 20/5 mg: 10% Placebo: 7%
Body, 2002[94]	Not specifically mentioned	Back pain was reported significantly more frequently by women in the alendronate group (19%) than by those in the teriparatide group (6%, $p = 0.012$)	Not specified
Bone, 1997[95]	No significant difference between treatment groups	20% of women in the 1 mg group, 26% in the 2.5 mg group, 17% in the 5 mg group and 23% in the placebo group suffered adverse effects which were suspected to be drug related	Alendronate 1 mg: 9% Alendronate 2.5 mg: 9% Alendronate 5 mg: 14% Placebo: 10%
Bone, 2000[52]	Occurred in 27% of women receiving alendronate, 30% receiving oestrogen, 34% receiving combination therapy and 22% in the placebo group (no significant difference between treatment groups)	None attributed to alendronate. Oestrogen, alone or in combination with alendronate, was frequently associated with complaints such as breast pain and weight gain	Alendronate: 6% Oestrogen: 10% Combination therapy: 9% Placebo: 10%
Carfora, 1998[96]	Episodes of nausea, dyspepsia, mild gastro-oesophagitis and abdominal pain appeared during the first 15 months of treatment with 20 mg of alendronate (no indication given of number of women affected)	Cutaneous rash was associated with alendronate (no indication given of number of women affected)	Not specified
Chesnut, 1995[54]	GI side-effects included nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain; they occurred mainly in the first year of treatment with 40 mg alendronate. Nine women receiving alendronate withdrew because of upper GI adverse events: seven of these were receiving 40 mg per day, and only one less than 20 mg per day	The only non-GI side-effect associated with alendronate was skin rash. One woman withdrew from the 20 mg group because of a rash which was believed to be alendronate related	Alendronate: 6% Placebo: 29%

continued

TABLE 138 *Alendronate: toxicity (cont'd)*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Dursun, 2001[97]	States only that no side-effects were serious enough to discontinue medication	States only that no side-effects were serious enough to discontinue medication	None
EPIC study[71]	At 4 years, the number of women suffering upper GI adverse events was similar in all groups, ranging between 37 and 46%	At 4 years, drug-related adverse events (including upper GI adverse events) had occurred in 11% of women in the 5 mg group, 16% in the 5 mg/placebo group, 15% in the 2.5 mg group and 9% in the 2.5 mg/placebo group, compared with 13% in the placebo group and 88% in the oestrogen–progestin group	Number not specified but said to be similar in the alendronate and placebo groups
FIT: women with pre-existing fractures[98]	Upper GI problems were experienced by 41% of women in the treatment group and 40% of women in the control group ($p = 0.67$). The rate of events did not increase after the dose was increased to 10 mg	Not specified	Alendronate: 8% Placebo: 10%
FIT: women without pre-existing fractures[99]	Upper GI problems were experienced by 48% of women in the treatment group and 47% of women in the control group	Not specified	Alendronate: 10% Placebo: 10%
Greenspan, 2002[60]	33% of women in the alendronate group and 35% in the placebo group reported upper GI adverse events; 0.6% and 1.9%, respectively, reported serious upper GI adverse events	93% of women in each group reported clinical adverse experiences (including upper GI adverse events)	Not specified
Liberman, 1995[100,110]	All four groups had similar rates of adverse upper GI events (37–42%). Such events led to withdrawal in 2.0% of those in the placebo group, 3.5% of those taking 5 mg, 1.0% of those taking 10 mg and 2.0% of those taking 20/5 mg.[a] There was no evidence of an increased incidence of serious or severe adverse oesophageal effects in the treatment groups compared with the placebo group. As severe oesophagitis has been associated with alendronate use, the authors suggest that their results are due primarily to the fact that the trial subjects had regular follow-up visits with frequent reinforcement of dosing instructions, but also recognise that trial participants generally have fewer coexisting conditions than normal patients	90% in the 5 mg group, 89% in the 10 and 20/5 mg groups, and 90% in the placebo groups suffered any clinical adverse event. 28% in the 5 mg group, 27% in the 10 mg group, 31% in the 20/5 mg group and 25% in the placebo group suffered adverse events considered by investigators blinded to treatment to be possibly, probably or definitely drug related	Alendronate 5 mg: 5% Alendronate 10 mg: 4% Alendronate 20/5 mg: 8% Placebo: 6%

continued

TABLE 138 *Alendronate: toxicity (cont'd)*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Lindsay, 1999[101]	Incidence of potentially drug-related GI adverse events was identical in both groups at 10.7%	Adverse effects were evenly distributed between the two groups. Back pain was the only adverse effect that was significantly more common in the intervention group (10% vs 3%)	Alendronate: 4% Placebo: 7%
Pols, 1999[102]	There were no significant differences between the groups in the overall incidence of upper GI adverse events (alendronate 21.3%, placebo 19.3%), or of specific upper GI adverse events such as abdominal pain, dyspepsia and nausea	No statistically significant differences were found in the overall incidence of adverse effects (alendronate 67.1%, placebo 69.7%), adverse events considered by the investigator to be possibly, probably or definitely drug related (19.1% vs 18.0%) or adverse events resulting in permanent discontinuation of study medication (6.4% vs 5.6%). Serious adverse events were also equally common between the groups (alendronate 6.5%, placebo 6.3%)	Not specified
Rossini, 1994[103]	No AEs were experienced during the 6 months of alendronate treatment	No adverse events were experienced during the 6 months of alendronate treatment	None

[a] Additional information obtained from Liberman and Hirsch (1996).[226]
GI, gastrointestinal.

TABLE 139 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Ishida, 2001[118]	Japan	1 year	BMD	Postmenopausal women with severe osteoporosis	Not stated	Rx1: 200 mg per day oral etidronate for days 1–14 of a 3-month cycle Rx2: 0.625 mg per day CEE + 2.5 mg per day medroxyprogesterone Rx3: 20 IU per week eel calcitonin Rx4: 1 μg per day alfacalcidol Rx5: 45 mg per day vitamin K_2	No treatment
Iwamoto, 2001[119]	Japan	2 years	BMD	Postmenopausal women with osteoporosis	65.2	Rx1: 200 mg per day oral etidronate for days 1–14 of a 3-month cycle Rx2: 45 mg per day vitamin K_2	2 g per day calcium lactate
Lyritis, 1997[120]	Greece	4 years	BMD	Postmenopausal women with severe osteoporosis (at least one non-traumatic vertebral collapse, and *T*-score ⩽–2)		2 μg per day 1,25-dihydroxyvitamin D_3 on days 1–5, 400 mg per day oral etidronate + 500 mg per day calcium for days 6–25, and 500 mg per day calcium for days 26–90 of a 90-day cycle	2 μg per day 1,25-dihydroxyvitamin D_3 on days 1–5, and 500 mg per day calcium for days 6–90 of a 90-day cycle
Montessori, 1997[121]	The Netherlands	3 years	BMD	Postmenopausal women with osteopenia (lumbar *Z*-score <–1), 36% of whom had vertebral fracture on entry	62.5 (45–73)	400 mg per day oral etidronate for days 1–14, and 500 mg per day calcium for days 15–90 of a 90-day cycle	500 mg per day calcium
Pacifici, 1988[122]	USA	2 years	Bone mineral content	Women with osteoporosis or osteopenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)	58 (26–80)	Rx1: 500 mg per day potassium phosphate on days 1–3, and 200 mg per day oral etidronate on days 4–17 of a 73-day cycle Rx2: 0.625 mg per day conjugated oestrogens on days 1–25, and 10 mg per day MPA on days 15–25 each month All subjects received 1 g per day calcium carbonate throughout	1 g per day calcium carbonate

continued

TABLE 139 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Storm, 1990[123]	Denmark	3 years	Bone mineral content at lumbar spine and distal non-dominant forearm; spinal deformity index; loss of height; rate of new vertebral fractures	Postmenopausal women with severe osteoporosis (at least one but no more than four atraumatic vertebral crush fractures)	68.3 (56–75)	400 mg per day oral etidronate for weeks 1–2 of a 15-week cycle + 500 mg per day elemental calcium + 400 IU per day vitamin D	Placebo + 500 mg per day elemental calcium + 400 IU per day vitamin D
Watts, 1990[124]	USA	2 years as RCT	Spinal BMD; rate of new vertebral fractures	Postmenopausal women with severe osteoporosis (at least one but no more than four vertebral crush fractures)	65.1	Rx1: 2g per day sodium–potassium phosphate on days 1–3, placebo on days 4–17, and 500 mg per day elemental calcium on days 18–91 of a 91-day cycle Rx 2: 400 mg per day oral etidronate on days 4–17, and 500 mg per day elemental calcium on days 18–91 of a 91-day cycle Rx3: 2 g per day sodium–potassium phosphate on days 1–3, 400 mg per day oral etidronate on days 4–17, and 500 mg per day elemental calcium on days 18–91 of a 91-day cycle	Placebo + 500 mg per day elemental calcium on days 18–91 of a 91-day cycle
Wimalawansa, 1998[125]	UK	4 years	BMD	Postmenopausal women with severe osteoporosis (spinal *T*-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)	64.9 (58–72)	Rx1: 0.625 mg per day Premarin + 150 μg Norgestrel for 12 days per month Rx2: 400 mg per day oral etidronate for weeks 1–2 of a 12-week cycle Rx3: 0.625 mg per day Premarin + 150 μg Norgestrel for 12 days/month + 400 mg per day oral etidronate for weeks 1–2 of a 12-week cycle All subjects received 1 g/day elemental calcium and 400 U per day vitamin D	1 g per day elemental calcium and 400 U per day vitamin D

TABLE 140 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Ishida, 2001[118]	Postmenopausal women with established osteoporosis	Not given	No details	Not stated	Published as abstract only
Iwamoto, 2001[119]	Women >5 years after the menopause with osteoporosis by the Japanese criteria[227]	History of HRT; having ever taken medication that affects bone metabolism	Comparable	A reduction of >20% in anterior, middle or posterior vertebral height compared with neighbouring vertebrae; or middle/anterior or middle/posterior height <0.8; or anterior/posterior height <0.75	The study was not stated to be blinded, and therefore was presumably open-label, although this is not stated
Lyritis, 1997[120]	Postmenopausal women with at least one non-traumatic vertebral collapse, low BMD (*T*-score <–2) and normal biochemical bone markers	Treated with bone-acting drugs in the year before inclusion in the study; secondary osteoporosis	Comparable	A reduction of ⩾20% in the anterior, middle or posterior height of any vertebral body, accompanied by an approximate reduction in area of ⩾10–20%	–
Montessori, 1997[121]	Women aged <75 years, ambulant and active, postmenopausal for ⩾1 year, with a lumbar spine *Z*-score <–1	Systemic treatment with oestrogens, androgens, vitamin D, calcium in pharmacological doses (>1 g per day), calcitonin or (other) bisphosphonates in the previous year; secondary osteoporosis or other forms of metabolic bone disease; active GI or liver disease; renal disease; active cancer within the past 3 years; alcoholism	Broadly comparable. Although the mean time since menopause was shorter in the etidronate group (176 vs 181 months) and there was a higher proportion of women with prevalent vertebral fractures in the control group (43.6% vs 28.2%), these differences were not statistically significant, and the groups were comparable in terms of age, height, weight and BMD	A reduction of ⩾20% in anterior, middle or posterior height, plus a reduction of ⩾10% in area in a previously unfractured vertebra	Although this was an open trial, the radiologists who assessed the spinal radiographs were blinded to treatment status

continued

TABLE 140 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Pacifici, 1988[122]	White women with at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation by quantitative computer tomography	Conditions known to influence calcium metabolism; contraindications to the study medications	Baseline characteristics were not presented in relation to the 35 women who dropped out during the first year of the study, and there is no information regarding the comparability of all groups at entry	Compression fractures: a loss of posterior height >15% compared with the mean of the posterior height of the nearest (above and below) intact vertebrae. Wedging and biconcave fractures: a loss of anterior and central height >20% compared with the posterior height of the same vertebra	–
Storm, 1990[123]	Postmenopausal women with at least one but no more than four atraumatic vertebral crush fractures and radiographically confirmed demineralisation of vertebrae	Secondary causes of osteoporosis (e.g. hyperparathyroidism, Paget's disease of bone or renal osteodystrophy); impairment of renal, cardiac or thyroid function; history of therapy with corticosteroids, oestrogens, calcitonin, calcium or vitamin D for ⩾3 months during the 6 months preceding study entry, or any such treatment during the 2 months preceding study entry; ever received fluoride or bisphosphonate therapy	Comparable	A reduction of ⩾20% in anterior, middle or posterior height (or all three), plus a reduction in area of ⩾10%	–
Watts, 1990[124]	Healthy white and Asian women with osteoporosis (defined as at least one but no more than four vertebral compression fractures plus radiographic evidence of vertebral osteopenia) who had been postmenopausal for ⩾12 months	Treatment with oestrogens, glucocorticoids, androgens, anabolic steroids, phosphate or pharmacological doses of calcium (>1 g per day) or vitamin D (>1000 IU per day) in the previous 6 months or with a thiazide diuretic in the previous 2 months; ever treated with fluoride, bisphosphonates or calcitonin; aged >75 years; weight <40 or >80 kg; secondary osteoporosis; medical conditions that might confound study participation (i.e. active rheumatoid arthritis, active GI or liver disease, chronic alcoholism or renal impairment)	Baseline characteristics were not given for the six women who withdrew immediately after randomisation	A reduction of ⩾20% in anterior, middle or posterior height, plus reduction of ⩾10% in area in a previously unfractured vertebra	Exceptions to the stated entry criteria were granted to nine women whose weight exceeded 80 kg and to five women whose age exceeded 75 years

continued

TABLE 140 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Wimalawansa, 1998[125]	Postmenopausal women with at least one but no more than four atraumatic thoracic vertebral crush fractures and spinal *T*-score <–2	Surgical menopause; secondary osteoporosis or other medical conditions that can affect the skeleton; medications that affect calcium metabolism within the previous 3 years; taking HRT, anabolic steroids, glucocorticoids, calcitonin, fluoride or bisphosphonates at any time since the menopause	Comparable	A reduction of ⩾20% in anterior, middle or posterior vertebral height plus a reduction of ⩾15% in area in a previously unaffected vertebra. Further deterioration in the height or area of a previously affected vertebra was not considered a new fracture	–

TABLE 141 *Studies of etidronate in women with postmenopausal osteoporosis or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Ishida, 2001[118]	1	1	1	1	3	1	8/18 (44)	Total = 183	Not stated	Not specified
Iwamoto, 2001[119]	1	1	1	3	0	3	9/15 (60)	Rx1: 25 Rx2: 23 Rx3: 24	Not stated	Not specified
Lyritis, 1997[120]	1	1	3	3	1	3	12/18 (67)	Rx: 50 C: 50	Rx: 78% C: 70%	Not specified
Montessori, 1997[121]	2	3	3	3	1	3	15/18 (83)	Rx: 40 C: 40	Rx: 88% C: 73%	Pharmaceutical company
Pacifici, 1988[122]	1	1	2	1	0	3	8/15 (53)	128	55% overall	Not specified
Storm, 1990[123]	2	3	2	3	1	3	14/18 (78)	Rx: 33 C: 33	Rx: 61% C: 61%	Pharmaceutical company
Watts, 1990[124]	2	3	3	3	1	3	14/18 (78)	Rx1: 107 Rx2: 105 Rx3: 107 C: 104	Rx1: 82% Rx2: 88% Rx3: 87% C: 87%	Pharmaceutical company
Wimalawansa, 1998[125]	2	3	2	3	1	3	14/18 (78)	Rx1: 18 Rx2: 17 Rx3: 19 C: 18	Rx1: 83% Rx2: 82% Rx3: 79% C: 78%	Not specified

TABLE 142 *Studies of etidronate in women with normal or unspecified BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Herd, 1997[62]	UK	2 years	BMD	Ambulatory white women at least 1 year but no more than 10 years postmenopausal with BMD between 0 and –2 SD of normal values for a 50-year-old woman measured in the local population	55 (37–66)	400 mg per day oral etidronate for days 1–14, and 500 mg per day elemental calcium for days 15–90 of a 90-day cycle	Placebo for days 1–14, and 500 mg per day elemental calcium for days 15–90 of a 90-day cycle
Meunier, 1997[67]	France	2 years	Lumbar BMD	Early postmenopausal women with normal BMD (Z-score between +2 and –2) who had not undergone hysterectomy or bilateral oophorectomy	52.7 (45–57)	400 mg per day oral etidronate for days 1–14, and 500 mg per day calcium for days 15–91 of a 91-day cycle	Placebo for days 1–14, and 500 mg per day calcium for days 15–91 of a 91-day cycle
Pouilles, 1997[70]	France	2 years	Lumbar BMD	Postmenopausal, HRT-naive, women	59.2 (45–60)	400 mg per day oral etidronate for days 1–14, and 500 mg per day calcium for days 15–91 of a 91-day cycle	Placebo for days 1–14, and 500 mg per day calcium for days 15–91 of a 91-day cycle

TABLE 143 *Studies of etidronate in women with normal or unspecified BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Herd, 1997[62]	Ambulatory white women at ⩾1 but ⩽10 years postmenopausal with BMD between 0 and –2 SD of normal values for a 50-year-old woman measured in the local population	Prevalent vertebral, hip or wrist fracture (unless related to severe trauma); history of any generalised bone disease, including hyperparathyroidism, Paget's disease of bone, renal osteodystrophy or any other congenital bone disease: any history of cancer within the past 5 years (except for epitheliomas or skin cancer); evidence of significant psychiatric or organic disease; any physical condition that would prevent the patient from completing the study; any laboratory abnormalities; treatment with corticosteroids, anabolic drugs, calcitonin, vitamin D (>400 U per day), oestrogens and/or progestogens within 6 months before recruitment; previous treatment with fluoride or any bisphosphonate	Comparable	Not given	–
Meunier, 1997[67]	Ambulatory, active Caucasian women between 45 and 90 kg and within 15% of their normal BMI; within 6–60 months of the menopause, and with a normal BMD (*Z*-score between + 2 and –2)	Any disease known to affect bone metabolism; bilateral oophorectomy or hysterectomy; prolonged treatment with calcitonin, vitamin D (>400 U per day), elemental calcium (>500 mg per day), corticosteroids or anabolic steroids, within the past 6 months; treatment with oestrogens and/or progestogens within the past year; previously treated with any bisphosphonate or a therapeutic dose of fluoride	Comparable	NA	There was a subsequent 12-month follow-up period during which women who had completed the study received elemental calcium 500 mg per day. 37 women entered the follow-up study (16 from the etidronate and 21 from the placebo group) and 35 completed the study. Two withdrew (one subject from the former placebo group disliked the taste of calcium, and one from the former etidronate group decided to commence HRT)

continued

TABLE 143 *Studies of etidronate in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Pouilles, 1997[70]	Ambulatory, active Caucasian women aged 45–60 years, weighing 45–80 kg and within 20% of their normal BMI; within 6–60 months of natural or surgical menopause, who had not been treated with HRT	Documented history of alcoholism; evidence of any bone metabolism disorder; undergoing treatment that might interfere with bone metabolism	The groups were comparable at baseline, except that the etidronate group had a slightly lower mean lumbar spine BMD than the placebo group	NA	–

TABLE 144 *Studies of etidronate in women with normal or unspecified BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Herd, 1997[62]	1	1	3	3	0	1	9/15 (60)	Rx: 75 C: 77	Rx: 85% C: 92%	Probably pharmaceutical company
Meunier, 1997[67]	1	1	3	3	1	0	9/15 (60)	Rx: 27 C: 27	Rx: 93% C: 89%	Pharmaceutical company
Pouilles, 1997[70]	1	1	3	2	1	0	8/15 (53)	Rx: 54 C: 55	Rx: 83% C: 84%	Not specified

TABLE 145 *Etidronate: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Herd, 1997[62]	Nausea, dyspepsia and diarrhoea were reported by more subjects in the placebo group (22%) than in the etidronate group (12%)	The most frequently reported adverse events were infection (primarily respiratory tract infections) and back pain; these occurred with similar frequency in both groups. 11% of the etidronate group and seven (9%) in the placebo group reported serious adverse events	Etidronate: 7 Placebo: 0
Ishida, 2001[118]	No data	No data	No data
Iwamoto, 2001[119]	No specific data	Adverse events (e.g. GI symptoms) occurred, primarily during the first 4 weeks of treatment, in 20% of the etidronate group and 8% of the calcium group	No data
Lyritis, 1997[120]	None reported	Adverse reactions were said to be minimal in both groups during the whole treatment period	Withdrawals were mostly due to patient non-attendance and not attributed to adverse drug effects
Meunier, 1997[67]	No severe GI adverse events were reported. Mild abdominal pain occurred in five subjects (four in the etidronate and one in the placebo group), all of whom had a prestudy history of GI problems; they were all intolerant of the calcium supplement	Overall, the majority of adverse events that were reported were mild in severity and comparable in incidence between the groups	Etidronate: 0 Placebo: 7%
Montessori, 1997[121]	Common adverse events in both groups included heartburn, constipation, abdominal cramps and diarrhoea	Overall, adverse events were mostly mild and evenly distributed over both groups. The two cases of cancer in the control group were considered unrelated to study medication	Only one subject withdrew because of an adverse event (severe diarrhoea) almost immediately after enrolment. This subject's group was not given
Pacifici, 1988[122]	None reported	Significant side-effects were said to occur only in the hormone group, and consisted primarily of pelvic congestion and cyclic bleeding; it is not stated how many women were affected	None
Pouilles, 1997[70]	The adverse event profiles of etidronate and placebo were said to be similar, although more digestive adverse events occurred in the etidronate group	Overall, 92 women (84%) experienced one or more adverse events (46 in each group)	Etidronate: 2% Placebo: 0

continued

TABLE 145 *Etidronate: toxicity (cont'd)*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Storm, 1990[123]	None reported	No significant side-effects were observed related to etidronate	None
Watts, 1990[124]	5–6% in all groups suffered nausea during days 1–17 (the phosphate/placebo and etidronate/placebo phases of the cycle); however, during days 1–3 (the phosphate/placebo phase), 39% of subjects receiving phosphate suffered diarrhoea compared with 9% of those receiving placebo	Overall, adverse effects were mild, generally infrequent and comparably distributed between the treatment groups	Etidronate only: 3% Phosphate only: 1% Etidronate–phosphate: 1% Placebo: 2%
Wimalawansa, 1998[125]	Six women (17%) complained of nausea following etidronate administration; the symptoms improved with time, and they continued on treatment	23 women (32%) distributed through all the groups complained of minor side-effects attributable to calcium, but continued supplementation	HRT: 17% Etidronate: 12% Combination therapy: 21% Control: 17%

TABLE 146 *Studies of risedronate in women with osteoporosis or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Clemmesen, 1997[131]	Belgium, Denmark	2 years	Spinal BMD	Postmenopausal women with severe osteoporosis (at least one but no more than four vertebral fractures)	68 (53–81)	Rx1: 2.5 mg per day oral risedronate Rx2: 2.5 mg per day oral risedronate for 2 weeks followed by placebo for 10 weeks of a 12-week cycle All subjects received 1 g per day calcium	Placebo + 1 g per day calcium
Fogelman, 2000[24]	Europe	2 years	Lumbar BMD	Postmenopausal women with osteopenia or osteoporosis (lumbar *T*-score ⩽–2)	64	Rx1: 2.5 mg per day oral risedronate Rx2: 5 mg per day oral risedronate All subjects received 1 g per day elemental calcium	Placebo + 1 g per day elemental calcium

continued

TABLE 146 *Studies of risedronate in women with osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Harris, 1999[132]	USA	3 years	Incidence of new vertebral fractures; incidence of radiographically confirmed non-vertebral fractures; changes from baseline BMD	Postmenopausal women with severe osteoporosis (either at least two vertebral fractures or one vertebral fracture and lumbar spine *T*-score of –2)	69	Rx1: 2.5 mg per day oral risedronate Rx2: 5 mg per day oral risedronate All subjects received 1 g per day elemental calcium	Placebo + 1 g per day elemental calcium
McClung, 1998[133]	USA	18 months	Lumbar BMD	Postmenopausal women with osteopenia (*T*-score at lumbar spine <–2)	68	Rx1: 2.5 mg per day oral risedronate Rx2: 5 mg per day oral risedronate All subjects received 1 g per day elemental calcium	Placebo + 1 g per day elemental calcium
McClung, 2001[134]	Multinational	3 years	Hip fracture	Women with osteoporosis; women with osteoporosis or at least one non-skeletal risk factor for hip fracture	Osteoporotic group: 74 (70–79) elderly group: 83 (≥80)	Rx1: 2.5 mg per day oral risedronate Rx2: 5 mg per day oral risedronate All subjects received 1 g per day elemental calcium	Placebo + 1 g per day elemental calcium
Reginster, 2000[135]	Europe, Australia	3 years	Proportion of subjects with at least one incident vertebral fracture	Postmenopausal women with severe osteoporosis (at least two vertebral fractures)	71	Rx1: 2.5 mg per day oral risedronate Rx2: 5 mg per day oral risedronate All subjects received 1 g per day calcium	Placebo + 1 g per day calcium

TABLE 147 *Studies of risedronate in women with osteoporosis or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Clemmesen, 1997[131]	Healthy postmenopausal women aged 53–81 years, ⩾1 year past the menopause, with established postmenopausal osteoporosis (at least one, but no more than four, vertebral fractures) and at least three intact lumbar vertebrae	Oestrogen or calcitonin treatment within 6–12 months before study entry; bisphosphonate or fluoride treatment at any time; secondary causes of osteoporosis; receipt of medication with known influence on bone metabolism	Comparable	A reduction of ⩾15% (Belgium) or 25% (Denmark) in anterior-to-posterior wall ratio, or in anterior or posterior wall as compared with adjacent vertebrae. This use of different vertebral fracture thresholds in the two centres meant that a valid global fracture analysis could not be performed	The authors suggest that the bioavailability of the risedronate may have been impaired by giving it as gelatin capsules, by allowing non-dairy fluids in the period 1–2 hours before and after capsule intake and by allowing it to be taken 2 hours after a meal
Fogelman, 2000[24]	Women aged ⩽80 years, postmenopausal for ⩾1 year, with a mean lumbar spine *T*-score ⩽–2	History of hyperparathyroidism, hyperthyroidism or osteomalacia within 1 year of study entry; history of cancer; abnormalities that would interfere with the measurement of lumbar spine BMD by DXA; taking, or having taken within 6–12 months (depending on the medication) treatment known to influence bone metabolism, including an injection of vitamin D ⩾10,000 IU	Comparable; although a higher proportion of subjects in the 5 mg group than in the other groups had received previous treatment for osteoporosis, this was not statistically significant	Any of the vertebral height ratios <3 SD of the mean for the study population[228]	At nine of the 13 centres, the 2.5 mg group was discontinued by protocol amendment on the basis of efficacy and safety assessments from other RCTs
Harris, 1999[132]	Ambulatory women ⩽85 years, ⩾5 years after natural or surgical menopause, with either two or more radiographically identified vertebral fractures or one vertebral fracture and a lumbar spine *T*-score –2	Conditions that might interfere with the evaluation of spinal bone loss; having received drugs known to affect bone metabolism (e.g. calcitonin, calcitriol or cholecalciferol supplements within 1 month before study entry; anabolic steroids, oestrogen or oestrogen-related drugs, or progestins within 3 months; bisphosphonates, fluoride or subcutaneous oestrogen implants within 6 months)	Comparable	A new fracture: a loss of height of at least 15% in anterior, posterior or middle height in a vertebra that was normal at baseline, or semi-quantitatively an increase in grade from 0 to 1, 2 or 3. A worsening fracture: a change of ⩾4 mm in vertebral height since the previous radiograph, or a change of grade in a previously fractured vertebra	One arm, that taking 2.5 mg per day risedronate, was discontinued after 1 year. Of those subjects who withdrew from the study, a higher percentage of those in the placebo group than the 5 mg group had experienced incident vertebral fractures; this may have reduced the apparent treatment effect

continued

TABLE 147 *Studies of risedronate in women with osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
McClung, 1998[133]	Postmenopausal women with lumbar spine *T*-score <–2	Not stated	No data	NA	Published as an abstract only
McClung, 2001[134]	Women aged 70–79 years with osteoporosis (*T*-score at femoral neck <–4, or <–3 with at least one non-skeletal risk factor for hip fracture). Women aged ⩾80 years with at least one non-skeletal risk factor for hip fracture, or a *T*-score at femoral neck <–4 SD, or a *T*-score at femoral neck <–3 with a hip–axis length of ⩾11.1 cm	Any major medical illness; recent history of cancer; another metabolic bone disease within the previous year; important abnormalities in the results of routine laboratory tests; recent use of drugs known to affect bone; allergy to any bisphosphonate; history of bilateral hip fractures; any physical or mental condition that would preclude participation in a clinical trial	Comparable[221]	NA	Non-skeletal risk factors for hip fracture include difficulty standing from a sitting position, a poor tandem gait, a fall-related injury during the previous year, a psychomotor score of ⩽5 on the Clifton Modified Gibson Spiral Maze test, current smoking or smoking during the previous 5 years, previous hip fracture, maternal history of hip fracture, and a hip–axis length of ⩾11.1 cm
Reginster, 2000[135]	Ambulatory women ⩽85 years, ⩾5 years postmenopausal, with at least two radiographically confirmed vertebral fractures	Conditions that might interfere with evaluation of spinal osteoporosis; use of calcitonin, calcitriol or vitamin D supplements within 1 month before study entry; anabolic steroids, oestrogen or oestrogen-related drugs, or progestogen within 3 months; bisphosphonates, fluoride or subcutaneous oestrogen implants within 6 months)	Comparable	A loss of height of ⩾15% in anterior, posterior or middle height in a vertebra that was normal at baseline, or semi-quantitatively an increase in grade from 0 to 1, 2 or 3	The 2.5 mg risedronate group was discontinued after 2 years because other data showed that a 5 mg dose produced a more consistent effect in increasing BMD while having a safety profile similar to that of 2.5 mg

TABLE 148 *Studies of risedronate in women with osteoporosis or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Clemmesen, 1997[131]	1	3	3	3	1	2	13/18 (72)	Rx1: 44 Rx2: 44 C: 44	Rx1: 66% Rx2: 75% C: 70%	Not specified
Fogelman, 2000[24]	1	1	3	3	1	4	13/18 (72)	Rx1: 184 Rx2: 179 C: 180	Rx1: 40% Rx2: 78% C: 79%	Pharmaceutical companies
Harris, 1999[132]	3	3	3	3	3	3	18/18 (100)	Rx1: 817 Rx2: 821 C: 820	Rx1: 0% Rx2: 61% C: 56%	Pharmaceutical company
McClung, 1998[133]	1	1	3	1	1	0	7/15 (47)	Rx1: 212 Rx2: 216 C: 220	62% overall	Not specified
McClung, 2001[134]	1	1	1	3	3	0	9/15 (60)	Rx1: 3093 Rx2: 3104 C: 3134	Rx: 50% C: 51%	Pharmaceutical companies
Reginster, 2000[135]	1	1	3	3	3	3	14/18 (78)	Rx1: 410 Rx2: 408 C: 408	Rx1: 18% Rx2: 62% C: 54%	Pharmaceutical company

TABLE 149 *Study of risedronate in women with normal BMD or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (years)	Intervention/dose	Comparison(s)
Mortensen, 1998[68]	Denmark, USA	2 years	Lumbar BMD	Early postmenopausal women with normal BMD (Z-score within ± 2 SD) and no osteoporotic fractures	51.5	Rx1: continuous risedronate (5 mg per day oral risedronate) Rx2: cyclical risedronate (5 mg per day oral risedronate for the first 2 weeks of every calendar month, then placebo daily for the rest of the month)	Placebo

TABLE 150 *Studies of risedronate in women with normal BMD or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Mortensen, 1998[68]	Active ambulatory women weighing ⩾45 and ⩽90 kg, within 25% of normal weight and height values, and with normal lumbar spine BMD (*Z*-score +2 to –2) who were 6–60 months postmenopausal	Receiving any bisphosphonate, thyroid hormone therapy, glucocorticoids (⩾5 mg per day prednisone), anabolic agents, calcitonin, vitamin D (>400 IU per day), calcium (>1500 mg per day), diuretics, or anticonvulsants for >1 month in the previous 6 months, oestrogens and/or progestogens for >1 month in the past year or fluoride for >1 month ever; history of any generalised bone disease, including hyperparathyroidism, Paget's disease of bone, renal osteodystrophy, or any other acquired or congenital bone disease; documented history of alcohol or drug abuse; evidence of significant organic or psychiatric disease; evidence of established osteoporosis (e.g. documented atraumatic vertebral fracture, history of osteoporosis-related fracture of the hip or wrist); bilateral oophorectomy or any other type of artificially induced menopause	Comparable	A ⩾25% decrease, compared to baseline, in anterior, middle or posterior vertebral height	This was originally designed as a 1-year study. After 1 year, participants were offered three options: to discontinue from the study; to complete a second year without therapy; or to continue the blinded study for the second year followed by an additional year without treatment. The blind regarding treatment assignment was maintained throughout the study

TABLE 151 *Study of risedronate in women with normal BMD or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Mortensen, 1998[68]	1	1	3	3	0	3	11/15 (73)	Rx1: 37 Rx2: 38 C: 36	Rx1: 46% Rx2: 63% C: 56%	Pharmaceutical company

TABLE 152 *Risedronate: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Clemmesen, 1997[131]	Three women (7%) in each group reported upper GI adverse events that were moderate to severe. Three women (7%) in the cyclic risedronate group and one (2%) in the continuous risedronate group reported GI adverse events related to the oesophagus; all were judged to be mild to moderate in severity, and three of the four women had a previous medical history of oesophagitis	No serious adverse events (including GI events) were considered causally related to risedronate	14% overall (not attributed to groups)
Fogelman, 2000[24]	30% in the 2.5 mg group, 23% in the 5 mg group and 26% in the placebo group suffered upper GI symptoms (most commonly abdominal pain, suffered by 11–13%, and dyspepsia, suffered by 8–14%). The various symptoms were evenly distributed among treatment groups	93% of the 2.5 mg group, 95% of the 5 mg group and 96% in the placebo group suffered adverse events (including upper GI events); 11% of the 2.5 mg group, and 15% each of the 5 mg and placebo groups suffered serious adverse events	Risedronate 2.5 mg: 10% Risedronate 5 mg: 11% Placebo: 8%
Harris, 1999[132]	30% of the 5 mg group and 27% of the placebo group suffered upper GI adverse events (most commonly abdominal pain, suffered by 12–13%, and dyspepsia, suffered by 11–13%). Duodenitis was more common in the 5 mg group (1% vs 0.2%)	97% of the 5 mg group and 95% of the placebo group suffered adverse events (including upper GI events). 34% and 29%, respectively, suffered adverse events that were thought to be drug related, and 29% and 27%, respectively, suffered serious adverse events	Risedronate 5 mg: 17% Placebo: 17% Adverse events related to the digestive system accounted for 42% of withdrawals due to adverse events from the placebo group and 36% from the 5 mg risedronate group
McClung, 1998[133]	The incidence of mild to moderate upper GI adverse events was comparable between groups	No data	Risedronate: 8% Placebo: 11%
McClung, 2001[134]	22% each of the 2.5 mg and placebo groups, and 21% of the 5 mg group suffered upper GI adverse events (most commonly abdominal pain, suffered by 8–9%, and dyspepsia, suffered by 8%). The various symptoms were evenly distributed among treatment groups	89% of the 2.5 mg group, and 90% each of the 5 mg and placebo groups suffered adverse events (including upper GI events); 30% of the 5 mg group and 31% each of the 2.5 mg and placebo groups suffered serious adverse events	Risedronate 2.5 mg: 18% Risedronate 5 mg: 18% Placebo: 18%
Mortensen, 1998[68]	8% in the continuous risedronate group, 13% in the cyclic group and 11% in the placebo group suffered abdominal pain, and 16%, 24% and 28%, respectively, suffered dyspepsia	There was no difference between treatment and placebo groups in the incidence of adverse events. Reports of arthralgia were low, and similar in the placebo and risedronate groups	Continuous risedronate: 5% Cyclic risedronate: 8% Placebo: 8% Only one of the adverse events (hip arthralgia in a subject receiving cyclic risedronate) was considered possibly drug related

continued

TABLE 152 *Risedronate: toxicity (cont'd)*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Reginster, 2000[135]	23% of the 2.5 mg group, 27% of the 5 mg group, and 26% of the placebo group suffered upper GI adverse events (most commonly abdominal pain, suffered by 9–12%, and dyspepsia, suffered by 9–11%)	92% each of the 2.5 and 5 mg groups, and 91% each of the placebo group suffered adverse events (including upper GI events); 27% of the 2.5 mg group, 28% of the 5 mg group and 32% of the placebo group suffered adverse events that were considered to be drug-related	Risedronate 2.5 mg: 13% Risedronate 5 mg: 15% Placebo: 20%

TABLE 153 *Studies of raloxifene in women with osteoporosis; general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Lufkin, 1998[137]	USA	1 year	BMD; biochemical markers; adverse events	Postmenopausal women with severe osteoporosis (low BMD and at least one non-traumatic vertebral fracture)	68.4 (45–75)	Rx1: 60 mg per day raloxifene Rx2: 120 mg per day raloxifene All subjects received 750 mg per day calcium + vitamin D to bring daily intake to 800 IU	Placebo + 750 mg per day calcium + vitamin D to bring daily intake to 800 IU
MORE study[138]	Multinational	3 years	Proportion of women with one or more new non-traumatic vertebral fractures; BMD	Postmenopausal women with osteoporosis (low BMD and/or vertebral fractures) (37% had at least one vertebral fracture at entry)	67 (31–80)	Rx1: 60 mg per day raloxifene Rx2: 120 mg per day raloxifene All subjects received 500 mg per day calcium + 400–600 IU vitamin D_3	Placebo + 500 mg per day calcium + 400–600 IU vitamin D_3

TABLE 154 *Studies of raloxifene in women with osteoporosis: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lufkin, 1998[137]	Healthy, fully ambulatory, postmenopausal women aged 45–75 years with osteoporosis (BMD for either lumbar spine or proximal femur of ⩽10th percentile for normal premenopausal females, and one or more non-traumatic vertebral fractures, defined as a decrease in vertical height of ⩾15% compared with adjacent vertebrae)	Any serious or chronic medical condition that might affect bone or calcium metabolism; history of DVT, thromboembolic disorders or cerebral vascular accident; history of cancer within the past 5 years (except for superficial skin cancer)	The groups were generally comparable at baseline except for minor but statistically significant differences in age and alcohol usage. Thus, the control group, while falling between the other two groups in age, had a notably higher level of alcohol usage	A decrease of ⩾15% in one or more of the anterior, posterior, left lateral and right lateral vertebral heights compared with baseline	–
MORE study[138]	Healthy women who were ⩾2 years postmenopausal with osteoporosis (defined as low BMD or radiographically apparent vertebral fractures). Group 1 had a femoral neck or lumbar spine *T*-score <–2.5. Group 2 had either low BMD plus one or more moderate or severe vertebral fractures, or two or more mild vertebral fractures, or at least two moderate fractures regardless of BMD (a mild fracture is defined as a 20–25% reduction, and a moderate fracture as a 25–40% reduction, in vertebral height)	Severe or long-term disabling conditions; bone disease other than osteoporosis; substantial postmenopausal symptoms or abnormal uterine bleeding; history of or suspected breast carcinoma at any time or of non-skin cancer in the previous 5 years; having taken an androgen, calcitonin or bisphosphonate within the past 6 months; taking oral oestrogen within the previous 2 months; fluoride therapy for >3 months during the previous 2 years or systemic glucocorticoid therapy for >1 month during the past year; having taken antiseizure drugs or pharmacological doses of cholecalciferol; history of thromboembolic disorders within the past 10 years (except in association with an injury); endocrine disorders requiring therapy (except for type 2 diabetes or hypothyroidism) serum creatinine levels >225 μmol l^{-1}; active renal lithiasis, abnormal hepatic function or untreated malabsorption; consumed more than 4 alcoholic drinks per day; pathological fractures; women from whom satisfactory thoracic and lumbar radiographs could not be obtained or with fewer than two lumbar and four thoracic vertebrae evaluable	Full baseline characteristics were provided only subdivided into the pooled placebo and pooled raloxifene groups[145]	A decrease in anterior, middle or posterior vertebral height of ⩾20% and ⩾4 mm	–

TABLE 155 *Studies of raloxifene in women with osteoporosis: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Lufkin, 1998[137]	1	1	3	2	1	3	11/18 (61)	Rx1: 48 Rx2: 47 C: 48	Rx1: 90% Rx2: 96% C: 94%	Pharmaceutical company
MORE study[138]	3	3	3	3	1	3	16/18 (89)	Rx1: 2557 Rx2: 2572 C: 2576	Rx: 78% C: 75%	Pharmaceutical company

TABLE 156 *Studies of raloxifene in younger postmenopausal women with normal to low BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
GGGF[39,56,63]	Western Europe	3 years with optional 2-year extension	Lumbar spine and total hip BMD; safety	Healthy postmenopausal women with normal to low BMD (*T*-score at lumbar spine +2.0 to –2.5); nearly 55% had osteopenia	55 (45–60)	Rx1: 30 mg per day raloxifene Rx2: 60 mg per day raloxifene Rx3: 150 mg per day raloxifene All subjects received 400–600 mg per day elemental calcium	Placebo + 400–600 mg per day elemental calcium
GGGG[39,63]	USA, Canada	3 years, with rerandomisation of part of the placebo group for a 2-year extension	Lumbar spine and total hip BMD; safety	Healthy postmenopausal women with normal to low BMD (*T*-score at lumbar spine +2.0 to –2.5)	(45–60)	Rx1: 30 mg per day raloxifene Rx2: 60 mg per day raloxifene Rx3: 150 mg per day raloxifene	Placebo
GGGH[39]	Not specified	3 years, with rerandomisation of part of the placebo group for a 2-year extension	Lumbar spine and total hip BMD; safety	Healthy hysterectomised women with normal to low BMD (*T*-score at lumbar spine +2.0 to –2.5)	(40–60)	Rx1: 60 mg per day raloxifene Rx2: 150 mg per day raloxifene Rx3: 0.625 mg per day Premarin	Placebo
Strickler, 2000[92]	USA	1 year	Quality of life	Healthy women who were 2–8 years postmenopause, with lumbar spine *T*-score +2 to –2.5	54.7 (47–60)	Rx1: 60 mg per day raloxifene Rx2: 150 mg per day raloxifene Rx3: 0.625 mg per day CEE All subjects received 520 mg per day calcium	Placebo + 520 mg per day calcium
Voss, 2002[47]	Europe, Israel, South Africa	6 months	Uterine bleeding patterns; endometrial thickness; uterine volume	Healthy ambulatory women ⩾2 years after their natural menopause	56.1 (⩽60)	60 mg per day raloxifene + placebo HRT	Continuous combined HRT (2 mg per day estradiol + 1 mg per day NETA) + placebo raloxifene

TABLE 157 *Studies of raloxifene in younger postmenopausal women with normal to low BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
GGGF[39,56,63]	Healthy women aged 45–60 years, menopausal for 2–8 years, *T*-score at lumbar spine +2.0 to –2.5	History of oestrogen-dependent tumours (except for *in situ* uterine tumours cured by hysterectomy); cancer (except for skin cancer) within the previous 5 years; had taken androgen, oestrogen, calcitonin or glucocorticoids within the previous 6 months; had ever taken a bisphosphonate or fluoride (except for dental prophylaxis); currently taking antiseizure medication, pharmacological doses of vitamin D or lipid-lowering drugs; history of thromboembolic disorders or of diabetes mellitus or other endocrine disorders requiring therapy (except for thyroid hormone replacement); abnormal renal or hepatic function; serious postmenopausal symptoms or abnormal uterine bleeding; excessive alcohol consumption (>4 drinks per day); drug abuse	Comparable	Not stated	–
GGGG[39,63]	Healthy women aged 45–60 years, menopausal for 2–8 years, *T*-score at lumbar spine +2.0 to –2.5	Not stated	Not stated	Not stated	–
GGGH[39]	Healthy hysterectomised women aged 40–60 years, *T*-score at lumbar spine +2.0 to –2.5	Not stated	Not stated	Not stated	Summary data only available in company submission
Strickler, 2000[92]	Healthy women aged 47–60 years who were 2–8 years postmenopause, with serum oestradiol level <73 pmol l^{-1} and lumbar spine *T*-score +2 to –2.5	Intolerable menopausal symptoms requiring therapy; uterine bleeding of unknown cause; BMI <18 kg m^{-2} or >31 kg m^{-2}; history of DVT; use of corticosteroids, oestrogen or progestin within the previous 6 months; chronic illness	Comparable	NA	–

continued

TABLE 157 *Studies of raloxifene in younger postmenopausal women with normal to low BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Voss, 2002[47]	Healthy ambulatory women aged ⩽60 years, ⩾2 years after their natural menopause	History of hysterectomy, ovariectomy, breast cancer or oestrogen-dependent cancer; any other cancer within the past 5 years; DVT or thromboembolism; liver disease; significant hypothyroidism or hyperthyroidism; not qualifying for therapy according to the prescribing information for E2 and NETA; endometrial thickness of >5 mm or any clinically significant endometrial or ovarian pathology; suspicious mammographic findings; severe postmenopausal symptoms requiring HRT use; treated with oestrogens/progestins in the past 6 months or hypolipidaemic drugs in the past 3 months	Comparable	NA	–

TABLE 158 *Studies of raloxifene in younger postmenopausal women with normal to low BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
GGGF[39,56,63]	1	3	3	3	3	3	16/18 (88)	Rx1: 152 Rx2: 152 Rx3: 147 C: 150	75% overall	Pharmaceutical company
GGGG[39,63]	1	3	3	3	3	3	16/18 (88)	Rx1: 136 Rx2: 134 Rx3: 138 C: 136	50% overall	Pharmaceutical company
GGGH[39]	1	3	1	1	3	1	10/18 (56)	Rx1: 152 Rx2: 157 Rx3: 158 C: 152	No data	Not stated
Strickler, 2000[92]	3	1	3	3	0	0	10/12 (83)	Rx1: 97 Rx2: 100 Rx3: 96 C: 105	No data	Pharmaceutical company
Voss, 2002[47]	3	3[a]	3	3	0	0	12/12 (100)	Rx1: 495 Rx2: 513	Rx1: 89% Rx2: 77%	Pharmaceutical company

[a] Assessors of endometrial/uterine end-points.

TABLE 159 *Raloxifene: toxicity*

Study	Oestrogen agonist and antagonist-related adverse effects	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
GGGF[39,56,63]	There was no significant difference in the proportion of women in the 60 mg group and the placebo group who reported either breast pain (3.3% and 2.0%, respectively) or hot flushes (26.3% and 22.7%, respectively), nor was there any significant difference between those groups in the proportions of women with an intact uterus reporting vaginal bleeding (3.0% and 2.2%, respectively)	There were no significant differences between the four groups in the proportion of women reporting any adverse event	There were no significant differences between the four groups in the proportion of women leaving the study because of an adverse event
GGGG[39,63]	Pooling of data with study GGGF found a statistically significant difference between the 60 mg and placebo groups only in relation to the proportion of women reporting hot flushes (25% vs 18%, respectively, $p = 0.04$); these were generally mild and did not increase study withdrawals[63]	At least one adverse event was reported by 88% of participants in the pooled studies GGGF and GGGG, with no difference between treatment groups[63]	No data
GGGH[39]	No data	No data	No data
Lufkin, 1998[137]	No data	There was no significant difference between groups in the numbers of adverse events reported. No major drug-related side-effects or adverse events were reported. Of the minor symptoms and signs, only arthralgia ($p = 0.027$) and dizziness ($p = 0.024$) were significantly more frequent in the raloxifene groups	Overall, eight women (5.4%) withdrew as a result of adverse events, but none of these were thought to be drug related

continued

TABLE 159 *Raloxifene: toxicity*

Study	Oestrogen agonist and antagonist-related adverse effects	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
MORE study[138]	Venous thromboembolic events were the only serious adverse effects believed to be causally related to raloxifene treatment. By 48 months, DVT had been reported in eight (0.3%) subjects in the placebo group, 20 (0.8%) in the 60 mg and 24 (0.9%) in the 120 mg raloxifene group. Pulmonary embolism had been reported in four (0.2%), 11 (0.4%) and 11 (0.4%), and retinal vein thrombosis in five (0.2%), two (0.1%) and three (0.1%) in the respective groups. In the 60 mg per day group, the risk of all venous thromboembolic events relative to the placebo group was 1.78 (95% CI 0.99 to 3.19). Hot flushes were the most common non-serious adverse event; these, with flu syndrome, leg cramps, endometrial cavity fluid and peripheral oedema, were significantly more common in the raloxifene group[143] Breast cancer was less common in the combined treatment groups than in the placebo group (RR 0.38, 95% CI 0.24 to 0.58)[143]		527 women (10.3%) in the raloxifene groups and 227 (8.8%) in the placebo group withdrew from the study because of an adverse event ($p = 0.04$). Hot flushes prompted withdrawal in 0.7%, 0.5% and 0.1% of the 60 mg, 120 mg and placebo groups, respectively
Strickler, 2000[92]	Not reported	Not reported	Not reported
Voss, 2002[47]	7% of the raloxifene group suffered vaginal bleeding or spotting, compared with 55% of the HRT group ($p < 0.01$)	None reported	24 women (4.8%) withdrew from the raloxifene group and 65 (12.7%) from the HRT group as a result of adverse events ($p < 0.001$). Vasodilatation was the main adverse event leading to withdrawal from the raloxifene group, causing withdrawal in six women (1.2%)

TABLE 160 *Studies of teriparatide in women with osteoporosis: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Body, 2002[94]	Multinational	Median 14 months	Change in lumbar spine BMD	Postmenopausal women with osteoporosis (spine or hip *T*-score <–2.5)	66	Once-daily subcutaneous teriparatide (40 μg per day) + 1000 mg per day calcium and 400–1200 IU per day vitamin D	Alendronate sodium (10 mg per day) + 1000 mg per day calcium and 400–1200 IU per day vitamin D
Cosman, 2001[148]	USA	3 years	BMD	Women with primary postmenopausal osteoporosis (spine or hip *T*-score of –2.5 and/or radiographically documented osteoporotic vertebral fracture) who had been receiving oestrogen/HRT for ⩾1 year before randomisation	60	Once-daily subcutaneous teriparatide [25 μg (400 IU) per day]	Placebo
Neer, 2001[149–151]	Multinational	Median 21 months	Incident vertebral fracture	Ambulatory women at least 5 years postmenopause with at least one moderate or two mild atraumatic radiographic vertebral fractures (women with fewer than two moderate fractures were also required to have a *T*-score ⩽–1)	70	Once-daily subcutaneous teriparatide (20 or 40 μg per day)	Placebo

TABLE 161 *Studies of teriparatide in women with osteoporosis: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Body, 2002[94]	Ambulatory women ⩾5 years postmenopause and aged 30–85 years, with no severe or chronically disabling conditions other than osteoporosis, and with lumbar spine or femoral neck *T*-score ⩽–2.5	Metabolic bone disorders; diseases affecting bone and mineral metabolism; carcinoma within the previous 5 years; nephrolithiasis or urolithiasis within the previous 2 years; malabsorption; significantly impaired renal or hepatic function; abnormalities of the lumbar spine prohibiting assessment of BMD at L2–L4; medications or drugs known to affect bone or mineral metabolism (e.g. androgens, anabolic steroids, bisphosphonates, calcitonin, glucocorticoids, oestrogens, fluoride) in the prior 2–24 months (depending on the drug); alcohol abuse; allergy or previous exposure to teriparatide, exogenous PTH, or PTH analogues	Comparable	NA	–
Cosman, 2001[148]	Postmenopausal women with primary osteoporosis (spine or hip *T*-score –2.5 and/or radiographically documented osteoporotic vertebral fracture) who had been receiving oestrogen/HRT for ⩾1 year before randomisation	Secondary causes of osteoporosis or medications (other than HRT) known to affect bone metabolism; active renal calculus disease with a renal stone within the past 10 years or multiple prior renal stones	The two groups were comparable in terms of height, weight, duration of oestrogen therapy, calcium intake, prevalent vertebral fractures and bone mass at all sites. However, the PTH group was significantly younger than the HRT group, although the groups were comparable in terms of number of years after menopause	A reduction of 15% in any of the vertebral heights compared with the baseline. Data were also analysed using a 20% definition as that subsequently became the standard in clinical trials	–
Neer, 2001[149–151]	Ambulatory women ⩾5 years postmenopause, with at least one moderate or two mild radiographically documented atraumatic vertebral fractures of the thoracic and lumbar spine; women with fewer than two moderate fractures had to have a hip or lumbar spine *T*-score of ⩽–1	Illnesses affecting bone or calcium metabolism; urolithiasis within the preceding 5 years; impaired hepatic function; serum creatinine concentration exceeding 2 mg dl^{-1}; alcohol or drug abuse; having taken drugs that alter bone metabolism within the previous 2–24 months (depending on the drug)	Comparable	Deformation of ⩾20% in a normal vertebra (worsening of pre-existing deformities was not analysed)	–

TABLE 162 *Studies of teriparatide in women with osteoporosis: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Body, 2002[94]	1	1	3	3	3	0	11/15 (73)	Rx1: 73 Rx2: 73	Rx1: 70% Rx2: 78%	Pharmaceutical companies
Cosman, 2001[148]	3	3	3	2	0	3	14/15 (93)	Rx: 27 C: 25	Rx: 78% C: 100%	Government agency
Neer, 2001[149–151]	1	3	3	3	3	1	14/18 (78)	Rx1: 541 Rx2: 552 C: 544	Not specified	Pharmaceutical company

TABLE 163 *Teriparatide: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Body, 2002[94]	Not specifically mentioned	Leg cramps were reported significantly more frequently by women in the teriparatide group (8%) than by those in the alendronate group (0%, $p = 0.012$)	Not specified
Cosman, 2001[148]	PTH was well tolerated, with no hypercalcaemia or nausea	One patient developed a urinary tract infection and a possible but undocumented kidney stone after 1.5 years. A large percentage of patients had mild discomfort at injection sites, with some erythema lasting for usually <1 hour after injections. Two women developed evidence of nodules at injection sites	Six out of 27 women (22%) randomised to PTH withdrew from the study during the 3 years of active treatment. Five withdrawals were due to adverse events (new diagnoses of other diseases: breast cancer, otosclerosis requiring fluoride treatment; depression, increased back pain attributed by the subject to PTH, and development of skin nodules at injection site. There were no withdrawals from the HRT-only group
Neer, 2001[149–151]	Nausea was reported by 18% and headache by 13% of women in the 40 μg group, but only 8% of those in the placebo group reported each of these symptoms ($p < 0.001$ and $p = 0.01$, respectively); the frequency of headache and nausea in the 20 μg group was similar to that in the placebo group	There were no significant differences between the groups in terms of numbers of deaths and hospitalisations, or numbers of women who developed cardiovascular disorders, urolithiasis or gout during the study. New or worsening back pain was reported by 17% of women in the 20 μg group, 16% in the 40 μg group and 23% in the placebo group. There were no cases of osteosarcoma. Although 9% of women in the 20 μg group reported dizziness and 3% reported leg cramps, compared with 6% and 1%, respectively, in the placebo group, the frequencies of these symptoms in the 40 μg group were similar to those in the placebo group	35 women (6%) in the 20 μg group, 59 (11%) in the 40 μg group and 32 (6%) in the placebo group withdrew because of an adverse event

TABLE 164 *Studies of calcium in women with osteoporosis: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Hansson, 1987[61]	Sweden	3 years	Spinal bone mineral content	Postmenopausal women with vertebral fractures	66±6[a]	Rx1: 1 g per day calcium (combination of bicarbonate, lactate and gluconate) Rx2: 10 mg per day sodium fluoride Rx3: 30 mg per day sodium fluoride	No treatment
Orimo, 1987[158]	Japan	Mean 1.7–2.1 years	Incidence of vertebral fractures	Elderly Japanese women with severe osteoporosis (decreased vertebral BMD and vertebral crush fractures)	72.4	1 g per day calcium (lactate or gluconate)	No treatment
Recker, 1996[159]	USA	Mean 4.3 years	Incidence of vertebral fractures; forearm bone mass changes	Elderly women with low self-chosen calcium intakes and prevalent vertebral fractures	74.9	1.2 g per day calcium (as calcium carbonate)	Placebo
Tilyard, 1992[160]	New Zealand	3 years	Rate of new vertebral fractures	Postmenopausal women with severe osteoporosis (at least one non-traumatic vertebral compression fracture)	63.7 (50–79)	1 g per day elemental calcium	0.5 μg per day oral calcitriol

[a] Mean ± SD.

TABLE 165 *Studies of calcium in women with osteoporosis: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Hansson, 1987[61]	Postmenopausal; at least one, and a maximum of three, vertebral compression fractures in the thoracic or lumbar spine, sustained during minor traumas	Fracture at L3 (the vertebral level used for determination of spinal BMD); known diseases; taking medication that could directly influence normal skeletal metabolism	Comparable in terms of age and BMD. No information given regarding prevalent vertebral fractures at baseline	Not given	–
Orimo, 1987[158]	Elderly Japanese women with decreased vertebral BMD and vertebral crush fractures	Not stated	There was a significant difference between the calcium and control groups in the number of fractures at baseline, which may have made calcium appear less effective than it actually was	A reduction of ⩾20% in the anterior, middle or posterior vertebral height compared with baseline	–
Recker, 1996[159]	Healthy ambulatory white women of European ancestry aged >60 years who were living independently and whose usual calcium intakes were estimated to be <1 g per day, with prevalent vertebral fractures	Diagnoses or treatments known to affect the skeleton	Comparable	A reduction of >20% in anterior or posterior height relative to baseline. Positive and negative calls of incident fracture by the algorithm were judged against the clinician's assessment, which was taken as the standard	For logistical reasons, it was necessary to randomise subjects to treatment without reference to their prevalent fracture status. Despite this, when they were broken down into fracture and non-fracture groups for analysis, the subgroups were found to be similar in age and customary calcium intake; the prevalent fracture groups were also comparable in terms of baseline bone mineral content

continued

TABLE 165 *Studies of calcium in women with osteoporosis: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Tilyard, 1992[160]	Fully ambulatory postmenopausal white women aged 50–79 years with osteoporosis (one or more non-traumatic vertebral fractures)	Evidence of any disease associated with osteoporosis or other major medical problems; history of using any drug known to cause or ameliorate osteoporosis (specifically including oestrogen)	Comparable	A reduction of ⩾15% in anterior or posterior vertebral height in any one year	Although randomisation codes were used to assign the women to treatment groups, both the subjects and the physicians were subsequently aware of the treatment assignment

TABLE 166 *Studies of calcium in women with osteoporosis: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Hansson, 1987[61]	1	1	1	1	0	1	5/15 (33)	Rx1: 25 Rx2: 25 Rx3: 25 C: 25	Rx1: 88% Rx2: 92% Rx3: 96% C: 76%	Research council; charitable funding
Orimo, 1987[158]	1	3	1	2	0	3	10/15 (67)	Rx1: 22 Rx2: 16 C1: 23 C2: 25	Not specified	Not specified
Recker, 1996[159]	1	3	3	3	0	2	12/15 (80)	Prevalent fracture group: Rx: 51 C: 41	Not specified	Dairy industry; government body; pharmaceutical company
Tilyard, 1992[160]	2	3	3	3	3	2	16/18 (89)	Rx: 308 C: 314	Rx: 71% C: 68%	Not specified

TABLE 167 *Studies of calcium in women with normal or unspecified BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Komulainen, 1998[162]	Scandinavia	5 years	BMD	Non-osteoporotic early postmenopausal women	52.7	Rx1: HRT (estradiol valerate 2 mg days 1–21, CPA 1 mg days 12–21) Rx2: vitamin D_3 [cholecaldiferol 300 IU (7.5 μg) per day] plus 93 mg per day Calcium^{2+}; no intake during June–August; in this group, during the 5th year, the vitamin D_3 dose was reduced to 100 IU per day because of observed adverse lipid changes during vitamin D_3 treatment Rx3: HRT + calcium and vitamin D_3 Rx 4: 500 mg per day calcium lactate (equivalent to Ca^{2+} 93 mg per day)	–
Recker, 1996[159]	USA	Mean 4.3 years	Incidence of vertebral fractures; forearm bone mass changes	Elderly women with low self-chosen calcium intakes without prevalent vertebral fractures	74.9	1.2 g per day calcium (as calcium carbonate)	Placebo
Reid, 1993[73]	New Zealand	2 years	BMD	Postmenopausal women without prevalent symptomatic vertebral fractures	58.5	1 g per day calcium (as calcium carbonate and calcium lactate–gluconate)	Placebo
Riggs, 1998[74]	USA	4 years	Bone loss from total skeleton, vertebrae and hip	Normal postmenopausal women (no history of osteoporotic fracture or radiographic evidence of vertebral fracture, Z-score >–2.0)	66.3±0.2[a] (61–70)	1.6 g per day calcium (as calcium citrate)	Placebo

[a] Mean ± SD.

TABLE 168 *Studies of calcium in women with normal or unspecified BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Komulainen 1998[162]			Comparable	NA	
Recker, 1996[159]	Healthy ambulatory white women of European ancestry aged >60 years who were living independently and whose usual calcium intakes were estimated to be <1 g per day, without prevalent vertebral fractures	Diagnoses or treatments known to affect the skeleton	Comparable	A reduction of >20% in anterior or posterior height relative to baseline. Positive and negative calls of incident fracture by the algorithm were judged against the clinician's assessment, which was taken as the standard	For logistical reasons, it was necessary to randomise subjects to treatment without reference to their prevalent fracture status. Despite this, when they were broken down into fracture and non-fracture groups for analysis, the subgroups were found to be similar in age and customary calcium intake; the prevalent fracture groups were also comparable in terms of baseline bone mineral content
Reid, 1993[73]	White women ⩾3 years postmenopause	History of disorders of calcium metabolism, including symptomatic vertebral fractures; renal, thyroid or hepatic dysfunction; current systemic disease; use of HRT within the previous 3 years; use of supraphysiological doses of any glucocorticoid for >6 months at any time; current use of any glucocorticoid, anticonvulsant medication or thiazide diuretic	Comparable	A reduction of >20% from baseline in anterior, middle or posterior vertebral height (in previously fractured vertebrae, a loss of height of ⩾4 mm was required)[163]	–

continued

TABLE 168 *Studies of calcium in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Riggs, 1998[74]	Fully ambulatory women aged 61–70 years and postmenopausal for ⩾10 years, with normal BMD for their age and gender (*Z*-score >–2.0)	History of osteoporotic fracture or radiologically identified prevalent vertebral fracture; history of renal lithiasis, impaired renal function, hypercalcaemia or hypercalciuria; any disease known to affect bone or calcium metabolism; receiving oestrogen, vitamin D >800 U per day or calcium >500 mg per day, or other drugs known to affect bone; history of using fluoride or bisphosphonates	Comparable	A change of >15% from baseline in anterior, middle or posterior height of a vertebra	–

TABLE 169 *Studies of calcium in women with normal or unspecified BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Komulainen, 1998[162]	1	1	2	3	1	0	8/15 (53)	Rx1: 117 Rx2: 114 Rx3: 114 Rx4: 117 C: 118	62	Health trust; pharmaceutical company
Recker, 1996[159]	1	3	3	3	0	2	12/15 (80)	Non-prevalent fracture group: Rx: 40 C: 59	Not specified	Dairy industry; government body; pharmaceutical company
Reid, 1993[73]	1	3	3	3	3	3	16/18 (89)	Rx: 61 C: 61	90% overall	Pharmaceutical company
Riggs, 1998[74]	1	1	3	3	1	3	12/15 (80)	Rx: 119 C: 117	Rx: 74% C: 76%	Government body; pharmaceutical companies

TABLE 170 *Calcium: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Hansson, 1987[61]	No data	No data	No data
Komulainen, 1998[162]		Serious adverse events were evenly distributed between the four treatment groups[229]	There were more withdrawals from the HRT (n = 42) and HRT + vitamin D groups (n = 30) than from the vitamin D (n = 13) and placebo (n = 11) groups. The most common reasons for non-compliance were menstrual disorders (n = 19) or headache (n = 14); these were not attributed to groups
Orimo, 1987[158]	No data	No data	No data
Recker, 1996[159]	Seven women (8%) in the calcium group and one (1%) in the placebo group complained of constipation	None mentioned	None
Reid, 1993[73]	No data	No data	Two withdrawals (3%) from the calcium group (due to renal calculus, and exacerbation of pre-existing dyspeptic symptoms) were considered potentially related to the study treatment
Riggs, 1998[74]	Nine women in the calcium group (8%) and two in the placebo group (2%) suffered abdominal cramping, constipation, bloating or diarrhoea	One woman in the calcium group (1%) and two in the placebo group (2%) suffered hypercalciuria; one woman in the placebo group suffered arthralgia and depression, and another renal stone	16 (ten in the calcium and six in the placebo group)
Tilyard, 1992[160]			27 women (8.6%) withdrew from the calcitriol group and 20 (6.5%) from the calcium group owing to adverse events ($p > 0.05$). 13 withdrawals from the calcitriol group and 12 from the calcium group were due to GI symptoms; two withdrawals from the calcitriol group were due to persistently elevated serum calcium

TABLE 171 *Studies of calcium plus vitamin D in women with normal or unspecified BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Baeksgaard 1998[51]	Denmark	2 years	Lumbar spine BMD	Healthy postmenopausal Caucasian women	62.5 (58–67)	Rx1: 1 g per day calcium (as calcium carbonate) + 14 μg (560 IU) per day vitamin D_3 Rx 2: 1 g per day calcium (as calcium carbonate) + 14 μg (560 IU) per day vitamin D_3 + multivitamin	Placebo
Chapuy, 1994[165]	France	3 years	Incidence of hip fracture	Mobile elderly women living in nursing homes or apartment homes for elderly people	84±6[a] (69–106)	1.2 g per day calcium (as tricalcium phosphate) + 20 μg (800 IU) per day vitamin D_3	Placebo
Chapuy, 2002[166]	France	2 years	Incidence of hip fracture	Mobile elderly women living in apartment homes for elderly people	85 (64–99)	Rx1: 1.2 g per day calcium (as tricalcium phosphate) + 20 μg (800 IU) per day vitamin D_3 in a fixed formulation Rx2: 1.2 g per day calcium (as tricalcium phosphate) + 20 μg (800 IU) per day vitamin D_3 as separate components	Placebo
Komulainen, 1998[162]	Scandinavia	5 years	BMD	Non-osteoporotic early postmenopausal women	52.7	Rx1: HRT (2 mg estradiol valerate on days 1–21, 1 mg cyproterone acetate on days 12–21) Rx2: vitamin D_3 [cholecaldiferol 300 IU (7.5 μg) per day] plus 93 mg per day Ca^{2+}; no intake during June–August; in this group, during the 5th year, the vitamin D_3 dose was reduced to 100 IU per day because of observed adverse lipid changes during vitamin D_3 treatment Rx3: HRT + calcium and vitamin D_3	500 mg per day calcium lactate (equivalent to Ca^{2+} 93 mg per day)

[a] Mean ± SD.

TABLE 172 *Studies of calcium plus vitamin D in women with normal or unspecified BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Baeksgaard, 1998[51]	Caucasian women aged 58–67 years, with good general health, postmenopausal (defined as cessation of menstrual bleeding for ⩾6 months)	Treatment with oestrogen or calcitonin during the previous 12 months or with bisphosphonates in the previous 2 years; presence of diseases known to affect bone metabolism; renal disease; hepatic disease; decreased function of the exocrine pancreas or any other state of malabsorption	No information given	Not given	–
Chapuy, 1994[165]	Mobile elderly women living in nursing homes or apartment homes for elderly people	Serious medical conditions; life expectancy >18 months; use of drugs known to alter bone metabolism (e.g. corticosteroids, thyroxine or anticonvulsant drugs) within the past year; treatment with fluoride salts for >3 months or with vitamin D or calcium during the previous 6 months or for >1 year within the past 5 years	Comparable	NA	–
Chapuy, 2002[166]	Mobile elderly women living in apartment homes for elderly people	Life expectancy <24 months; intestinal malabsorption, hypercalcaemia or chronic renal failure; use of drugs known to alter bone metabolism (e.g. corticosteroids, anticonvulsants or a high dose of thyroxine) within the past year; treatment with fluoride salts for >3 months, with bisphosphonates or calcitonin for >1 month, or with vitamin D (>100 IU per day) or calcium (>500 mg per day) during the previous 12 months	Comparable	NA	66% of subjects were suffering from both low vitamin D status and low calcium intake
Komulainen, 1998[162]			Comparable	NA	

TABLE 173 *Studies of calcium plus vitamin D in women with normal or unspecified BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Baeksgaard, 1998[51]	1	1	2	1	0	1	6/15 (40)	Rx1: 80 Rx2: 80 C: 80	83% overall	Pharmaceutical company
Chapuy, 1992[230], 1994[165]	1	1	3	3	3	0	11/15 (73)	Rx: 1635 C: 1635	54% in each group at 18 months	Government agencies; health insurance agency; pharmaceutical companies
Chapuy, 2002[166]	1	1	3	3	1	1	10/18 (56)	Rx1: 199 Rx2: 194 C: 190	Rx1: 73% Rx2: 71% C: 64%	Pharmaceutical company
Komulainen, 1998[162]	1	1	2	3	1	0	8/15 (53)	Rx1: 116 Rx2: 116 Rx3: 116 C: 116	Rx1: 64% Rx2: 89% Rx3: 74% C: 91%	Health trust; pharmaceutical company

TABLE 174 *Calcium plus vitamin D: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Baeksgaard, 1998[51]	No data	No data	No data
Chapuy, 1994[165]	No data	No data	40 women (3%) in the treatment group and 28 (2%) in the placebo group had GI symptoms (nausea, diarrhoea or epigastric pain) which led to discontinuation of treatment
Chapuy, 2002[166]	24 women (6%) receiving active treatment and 16 (8%) in the placebo group reported GI symptoms (nausea, diarrhoea, epigastric pains)	Three women (1%) in the active treatment group developed hypercalcaemia, one resulting from recent myeloma and the other two from hyperparathyroidism	GI symptoms led to discontinuation of treatment in three cases (0.5%) (not attributed to treatment groups)
Komulainen, 1998[162]		Serious adverse events were evenly distributed between the four treatment groups[229]	There were more withdrawals were from the HRT (n = 42) and HRT + vitamin D groups (n = 30) than from the vitamin D (n = 13) and placebo (n = 11) groups. The most common reasons for non-compliance were menstrual disorders (n = 19) or headache (n = 14); these were not attributed to groups

TABLE 175 *Studies of calcitriol in women with severe osteoporosis or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Aloia, 1985[168]	USA	2 years	BMD;[a] incidence of vertebral fracture;[a] biochemical measures;[a] bone biopsy[a]	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)	64.5 (50–80)	Oral calcitriol mean dose 0.8 μg per day + 400 IU per day vitamin D	400 IU per day vitamin D
Arthur, 1990[169]	USA	1 year	BMD	Postmenopausal women with radiographic evidence of osteopenia, 40% of whom had vertebral compression fractures at entry	66.4 (<60)	0.25–0.50 μg per day oral calcitriol + 1 g per day elemental calcium	50,000 U vitamin D_2 twice a week + 1 g per day elemental calcium
Caniggia, 1984[53]	Italy	1 year	Height;[a] vertebral fracture;[a] bone pain;[a] ambulancy;[a] biochemical parameters;[a] BMC and histomorphometry;[a] safety parameters[a]	Healthy postmenopausal women with severe osteoporosis (at least one vertebral crush fracture)	(54–74)	Rx1: 0.5 μg per day oral calcitriol Rx2: 0.5 μg per day oral calcitriol + estradiol valerate 2 mg per day Rx3: estradiol valerate 2 mg per day	Placebo
Falch, 1987[170]	Norway	2 years	Bone mass;[a] vertebral fractures;[a] fractures of long bones[a]	Postmenopausal women with established osteoporosis (fracture of distal left forearm)	59.6 (50–65)	0.5 μg per day calcitriol (reduced to 0.25 μg per day in 28% of cases)	400 IU per day vitamin D_3
Gallagher, 1989[87]	USA	1 year as RCT	Vertebral fracture rates	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)	63.2	0.5 μg per day oral calcitriol, increased to 0.75 or 1.0 μg per day at investigator's discretion	Placebo
Gallagher, 1990[171]	USA	2 years	Safety; BMD	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral fracture)	69.7 (50–78)	Oral calcitriol mean dose 0.62 μg per day + 400 IU per day vitamin D_2	Placebo + 400 IU per day vitamin D_2

continued

TABLE 175 *Studies of calcitriol in women with severe osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Ott, 1989[172]	USA	2 years	Change in bone mass	Postmenopausal women with established osteoporosis (at least two non-traumatic vertebral compression fractures)	67.5 (50–80)	Oral calcitriol 0.5–2.0 μg (mean dose at study end 0.43 μg per day; mean dose overall 0.52 μg per day; Ott SM: personal communication) + 1 g per day calcium	Placebo + 1 g per day calcium
Tilyard, 1992[160]	New Zealand	3 years	Rate of new vertebral fractures	Postmenopausal women with established osteoporosis (at least one non-traumatic vertebral compression fracture)	63.7 (50–79)	0.25 μg per day oral calcitriol	1 g per day elemental calcium

[a] Does not differentiate between primary and secondary outcome measures.

TABLE 176 *Studies of calcitriol in women with severe osteoporosis or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Aloia, 1985[168]	Healthy women aged 50–80 years with postmenopausal osteoporosis (at least one non-traumatic vertebral compression fracture)	Hepatic or renal disease; malignancy; malabsorption syndrome; parathyroid or thyroid disorders; inflammatory arthritis; alcoholism; overt vitamin D deficiency; history of renal lithiasis; allergy to tetracycline; insulin-dependent diabetes; previous long-term hospitalisation; any other disorder known to affect bone metabolism; intake of certain drugs (including glucocorticoids, anticonvulsants, oestrogens, sodium fluoride, calcium supplements and pharmacological doses of vitamin D)	Baseline characteristics were only given for the 27 women who completed the study, and there is no information regarding the comparability of all groups at entry	Not given	Study completers in the placebo group had more fractures than those in the intervention group at baseline, but this was not statistically significant. However, the authors admit that it is not known whether this difference could have influenced the outcome of the study

continued

TABLE 176 *Studies of calcitriol in women with severe osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Arthur, 1990[169]	Women aged >60 years with radiographic evidence of osteopenia	Hepatic or renal disease; malabsorption or surgery that might predispose to malabsorption; hypercalcaemia; malignancy; hyperthyroidism; alcoholism; significant immobilisation; use of anticonvulsants, heparin or steroids, including oestrogen	Baseline characteristics were only given for the ten women who completed the randomised study, and there is no information regarding the comparability of all groups at entry	Not given	–
Caniggia, 1984[53]	Healthy ambulatory women aged 54–74 years with symptomatic postmenopausal osteoporosis (marked radiolucency of the spine plus at least one crush fracture occurring spontaneously or after minimal trauma)	Overt vitamin D deficiency; malabsorption; treatment with adrenocortical steroids for ⩾3 months in the past 5 years, or with anticonvulsants, oestrogens, gestogens, androgens, anabolic drugs, thiazide diuretics, sodium fluoride, calcium and vitamin D during the past 6 months	Data relating to the comparability of the groups at baseline is provided only in relation to biochemical parameters; these show some variations between groups	None given	–
Falch, 1987[170]	Women aged 50–65 years who had sustained a fracture of the distal left forearm	Fractures caused by a fall from higher than standing position; previous fractures of the right forearm; endocrine disease; malabsorption; gastric surgery; nephrolithiasis; renal failure; regular intake of oestrogens, glucocorticoids or anticonvulsants; still menstruating	Comparable	Each vertebra was compared with the nearest cranial vertebra. If the anterior wedging or middle depression was <85% of the cranial vertebra, the vertebra was assigned a fracture score of 1; if both measurements were <85%, the fracture score was 2	–

continued

TABLE 176 *Studies of calcitriol in women with severe osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Gallagher, 1989[87]	Healthy postmenopausal women with definite evidence of one or more vertebral fractures with no history of trauma	Abnormal liver or renal function; obvious disease; drug history known to be associated with a disturbance of calcium metabolism; osteomalacia	Baseline characteristics were only given for the 62 women who had results that could be included in the analysis of fracture outcomes; no information was given regarding the comparability of all groups at entry	A decrease of 15% in anterior vertebral height from baseline	This study combines the data from two similar double-blind, placebo-controlled RCTs. At the end of the first year, all subjects from the placebo arm were crossed over to treatment; therefore, only the results of the first, placebo-controlled, year are reported here
Gallagher, 1990[171]	Postmenopausal women aged between 50 and 78 years with osteoporosis (one or more non-traumatic vertebral fractures)	Significant chronic disease such as renal failure, malignancy, GI abnormalities, hyperparathyroidism or hypoparathyroidism, acromegaly, Cushing's syndrome or arthritis; overt vitamin D deficiency; history of renal calculi, diabetes or alcoholism; prolonged immobilisation; osteomalacia; treatment with corticosteroids for >3 months, or with anticonvulsants, oestrogens, calcium supplements or vitamin D during the past 6 months, or sodium fluoride in the past year	Baseline characteristics were only given for the 40 women who completed the study, and there is no information regarding the comparability of all groups at entry	A reduction of 15% in anterior or posterior vertebral height	Although the study design was double-blind, the study nurse became unblinded as serum and urine calcium levels rose in the first few weeks of the study. However, it seems to be implied, but is not stated, that the outcome assessors were blinded to treatment allocation
Ott, 1989[172]	Ambulatory white postmenopausal women aged 50–80 years with at least two non-traumatic vertebral compression fractures	Abnormal laboratory test results; taking medication (other than calcium supplements) for treatment of osteoporosis; history of corticosteroid use, malnutrition, sarcoidosis, liver disease, rheumatoid arthritis, nephrolithiasis, renal disease or recent malignancy	Broadly comparable. However, the placebo group was more severely affected by vertebral fractures than the calcitriol group at baseline	A loss of anterior height of >15% resulting in an anterior/posterior ratio of <85%	–

continued

TABLE 176 *Studies of calcitriol in women with severe osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Tilyard, 1992[160]	Fully ambulatory postmenopausal white women aged 50–79 years with osteoporosis (one or more non-traumatic vertebral fractures)	Evidence of any disease associated with osteoporosis or other major medical problems; history of using any drug known to cause or ameliorate osteoporosis (specifically including oestrogen)	Comparable	A reduction of ⩾15% in anterior or posterior vertebral height in any one year	Although randomisation codes were used to assign the women to treatment groups, both the subjects and the physicians were subsequently aware of the treatment assignment

TABLE 177 *Studies of calcitriol in women with severe osteoporosis or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Aloia, 1985[168]	1	3	2	1	0	1	8/15 (53)	Rx: 17 C: 17	Rx: 71% C: 88%	Not specified
Arthur, 1990[169]	1	3	1	1	0	1	7/15 (47)	Rx: 4 C: 6	Rx: 75% C: 67%	Not specified
Caniggia, 1984[53]	1	1	1	1	0	1	5/15 (33) Rx3: 7	Rx1: 7 Rx2: 7 Rx1: 71% C: 7	Rx2: 71% Rx3: 100% C: 71%	Not specified
Falch, 1987[170]	1	3	2	3	1	3	13/18 (72)	Rx: 47 C: 39	Rx: 83% C: 95%	Not specified
Gallagher, 1989[87]	1	3	2	1	0	2	9/15 (60)	Rx: 38 C: 33	Rx: 87% C: 88%	Research body; pharmaceutical company
Gallagher, 1990[171]	3	1	2	1	0	2	9/15 (60)	Rx: 25 C: 25	Rx: 72% C: 88%	Pharmaceutical company
Ott, 1989[172]	3	1	2	3	1	2	12/18 (67)	Rx: 43 C: 43	Rx: 91% C: 86%	Research body; pharmaceutical company
Tilyard, 1992[160]	2	3	3	3	3	2	16/18 (89)	Rx: 314 C: 308	Rx: 68% C: 71%	Not specified

TABLE 178 *Study of calcitriol in women with normal BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Gallagher, 2001[58]	USA	3 years	BMD	Elderly women with normal (±2 SD) *Z*-score at femoral neck	71 ± 4[a] (65–77)	Rx1: 0.25 μg b.d. calcitriol Rx2: HRT (CEE 0.625 mg per day plus, in non-hysterectomised women, MPA 2.5 mg per day) Rx3: HRT plus calcitriol	Placebo

[a] Mean ± SD.

TABLE 179 *Study of calcitriol in women with normal BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Gallagher, 2001[58]	Women aged 65–77 years with normal femoral neck BMD (*Z*-score 2.0 to –2.0)	Severe chronic illness; primary hyperparathyroidism; active renal stone disease; had taken bisphosphonates, anticonvulsants, oestrogen, fluoride or thiazide diuretics in the previous 6 months	Comparable	Not given	The mean *T*-score at baseline was approximately –2.5

TABLE 180 *Study of calcitriol in women with normal BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Gallagher, 2001[58]	1	3	3	2	3	3	15/18 (83)	Rx1: 123 Rx2: 121 Rx3: 122 C: 123	Rx1: 82% Rx2: 83% Rx3: 84% C: 91%	Government agency (main funder); pharmaceutical companies

TABLE 181 *Calcitriol: toxicity*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Aloia, 1985[168]	None reported	Hypercalciuria occurred in all subjects treated with calcitriol; the authors felt that this could have been avoided by parenteral administration of the drug	None of the withdrawals seemed attributable to the treatment, although one withdrawal from the placebo group was because of dizziness and nausea believed by the subject to be caused by the 'drug'
Arthur, 1990[169]	None reported	Significant hypercalciuria was observed in both groups, and transient hypercalcaemia in one subject in the vitamin D_2 group. However, the subjects' renal function did not decline significantly over the course of the study	Not specified
Caniggia, 1984[53]	None reported	None reported	Not specified
Falch, 1987[170]	One woman in the calcitriol group and two in the vitamin D_3 group suffered abdominal pain	There were no significant differences between the two groups in relation to reported symptoms. In 11 women in the calcitriol group (28%), it was necessary to halve the initial dose of 0.50 μg calcitriol per day because total serum calcium exceeded 2.65 mmol l^{-1}	No withdrawals were attributed to drug-related adverse effects
Gallagher, 1989[87]	Not reported	Not reported	No withdrawals were attributed to treatment
Gallagher, 1990[171]	None reported	Hypercalcaemia and hypercalciuria occurred during the first few weeks of dosage titration, but no further problems occurred after the long-term maintenance dose had been reached. In addition, during the course of the study, to prevent hypercalcaemia, participants were advised to reduce their calcium intake to 600 mg per day	One woman (4%) withdrew from the treatment group because of nausea
Gallagher, 2001[58]	Major GI adverse events occurred in 16% of the calcitriol group, 11% of the oestrogen group, 12% of the combination therapy group and 18% of the placebo group	At least one episode of hypercalciuria occurred in 26% of the calcitriol group, 3% of the oestrogen group, 15% of the combination therapy group and 8% of the placebo group. 11 women had gallstones or cholecystitis: eight (3%) in the groups receiving oestrogen and three (1%) in the other groups. Four women in the oestrogen groups (1.6%) had DVT compared with one (0.4%) in the other groups	The major reasons given for discontinuing medication were bleeding problems (n = 21), breast tenderness (n = 13), other significant health problems (n = 21), lost interest in the study (n = –19), cerebrovascular incident/cerebral thrombosis/cerebral haemorrhage/transient ischaemic attack (n=15) and GI problems (n=14)

continued

TABLE 181 *Calcitriol: toxicity (cont'd)*

Study	Upper gastrointestinal adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Ott, 1989[172]	Comparable in both groups	No major side-effects of calcitriol were identified during the study. Minor symptoms (e.g. upper respiratory or urinary tract infections, back pain and indigestion) were similar in both groups. Although the treatment group had significantly higher serum and urine calcium values, renal function was not worse than in the placebo group	None
Tilyard, 1992[160]	No information was provided on signs or symptoms not sufficiently severe to warrant withdrawal from the study	No information was provided on signs or symptoms not sufficiently severe to warrant withdrawal from the study	27 women (8.6%) withdrew from the calcitriol group and 20 (6.5%) from the calcium group owing to adverse events ($p > 0.05$). 13 withdrawals from the calcitriol group and 12 from the calcium group were due to GI symptoms; two withdrawals from the calcitriol group were due to persistently elevated serum calcium

TABLE 182 *Studies of oestrogen in women with osteoporosis or osteopenia: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Alexandersen, 1999[50]	Denmark	96 weeks	BMD	Healthy postmenopausal women with osteopenia or osteoporosis (*T*-score ≤ -1), but without more than three vertebral fractures or a history of femoral fracture at enrolment (48% were osteoporotic and 52% osteopenic)	65 (60–70)	Rx1: combined continuous HRT (17β-estradiol matrix patch releasing 50 µg per day) plus oral NETA (1 mg per day) Rx2: oral monofluorophosphate equivalent to 20 mg per day fluoride Rx3: combined HRT and MFP All subjects received 1000 mg per day calcium	Placebo + 1000 mg per day calcium
Bone, 2000[52]	USA	2 years	Lumbar BMD	Hysterectomised postmenopausal women with lumbar spine BMD below 0.862 g cm^{-2} (Hologic) (mean *T*-score –2.5 ± 0.2)	61.4	Rx1: 10 mg per day oral alendronate Rx 2: 0.625 mg per day CEE Rx 3: 10 mg per day oral alendronate plus 0.625 mg per day CEE All subjects received 500 mg per day elemental calcium	Placebo + 500 mg elemental calcium
Caniggia, 1984[53]	Italy	1 year	Height;[a] vertebral fracture;[a] bone pain;[a] ambulancy;[a] biochemical parameters;[a] BMC and histomorphometry;[a] safety parameters[a]	Healthy postmenopausal women with severe osteoporosis (at least one vertebral crush fracture)	(54–74)	Rx1: 0.5 µg per day oral calcitriol Rx2: 0.5 µg per day oral calcitriol + estradiol valerate 2 mg per day Rx3: estradiol valerate 2 mg per day	Placebo
Ishida, 2001[118]	Japan	1 year	BMD	Postmenopausal women with severe osteoporosis	Not stated	Rx1: 200 mg per day oral etidronate for days 1–14 of a 3-month cycle Rx2: 0.625 mg per day CEE + 2.5 mg per day medroxyprogesterone Rx3: 20 IU per week eel calcitonin Rx4: 1 µg per day alfacalcidol Rx5: 45 mg per day vitamin K_2	No treatment

continued

TABLE 182 *Studies of oestrogen in women with osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Lindsay, 1990[65]	USA	2 years	BMD	Women with postmenopausal osteoporosis (low BMD + atraumatic vertebral crush fractures or vertebral deformities)	61.9	CEE (0.625 mg per day) plus, for women with an intact uterus, cyclic MPA (5 or 10 mg per day for 12–14 days per calendar month)	No treatment
Lufkin, 1992[173]	USA	1 year	Bone turnover assessed by biochemical markers and iliac bone histomorphometry;[a] BMD;[a] vertebral fracture rate[a]	Postmenopausal women with established osteoporosis (low BMD and at least one vertebral fracture)	64.8 (47–75)	0.1 mg transdermal 17β-estradiol on days 1–21 + 10 mg oral MPA on days 11–21 of a 28-day cycle	Placebo
Pacifici, 1988[122]	USA	2 years	Bone mineral content	Women with osteoporosis or osteopenia (at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation)	58 (26–80)	0.625 mg per day conjugated oestrogens for 25 days per month, 10 mg per day medroxyprogesterone on days 15–25 + 1000 mg per day calcium carbonate	1000 mg per day calcium carbonate
Recker, 1999[72]	USA	3.5 years	Spinal BMD	Healthy white women with osteoporosis or osteopenia (*T*-score $\leq$–1.13) without a history of hip fracture, and who did not smoke more than 10 cigarettes a day	73.3 (>65)	CEE (0.3 mg per day) plus medroxyprogesterone (2.5 mg per day)	Placebo

continued

TABLE 182 *Studies of oestrogen in women with osteoporosis or osteopenia: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Wimalawansa, 1998[125]	UK	4 years	BMD	Postmenopausal women with established osteoporosis (spinal *T*-score –2 and at least one but no more than four atraumatic thoracic vertebral crush fractures)	64.9 (58–72)	Rx1: 0.625 mg per day Premarin + 150 μg Norgestrel for 12 days per month Rx2: 400 mg per day oral etidronate for weeks 1–2 of a 12-week cycle Rx3: 0.625 mg per day Premarin + 150 μg Norgestrel for 12 days per month + 400 mg per day oral etidronate for weeks 1–2 of a 12-week cycle All subjects received 1 g per day elemental calcium and 400 U per day vitamin D	1 g per day elemental calcium and 400 U per day vitamin D
Zarcone, 1997[174]	Italy	64 months	BMD at lumbar spine; vertebral fractures	Postmenopausal women with osteoporosis (BMD at lumbar spine $\leqslant$0.88 g cm^{-2})	(45–63)	Rx1: 0.15 mg per day CEE Rx2: 0.3 mg per day CEE Rx3: 0.625 mg per day CEE	Placebo

[a] Does not differentiate between primary and secondary outcome measures.

TABLE 183 *Studies of oestrogen in women with osteoporosis or osteopenia: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Alexandersen, 1999[50]	Healthy women aged 60–70 years who had passed a natural menopause, and with a *T*-score of the distal third of the non-dominant forearm ≤–1	Taking, currently or in the year before randomisation, any medication known to influence bone metabolism; more than three vertebral crush fractures or a history of femoral fracture; BMI 30% above the ideal weight; renal insufficiency, hepatic failure or malignancy; smoking >10 cigarettes per day	Comparable	A reduction of > 20% in anterior, middle or posterior vertebral height	–
Bone, 2000[52]	Prior hysterectomy (to avoid any possible confounding effects of progestin therapy or withdrawal bleeding); lumbar spine BMD <0.862 g cm^{-2} as measured by Hologic densitometry equipment for at least three evaluable vertebrae in the L1–L4 region	Evidence of metabolic bone disease other than postmenopausal osteoporosis; low serum 25-hydroxyvitamin D concentration (<10 ng ml^{-1}); concomitant therapy with drugs that affect bone turnover (including bisphosphonates, calcitonin, fluoride); renal insufficiency; severe cardiac disease; history of recent major upper GI mucosal erosive disease (including significant upper GI bleeding, recurrent peptic ulcer disease, and oesophageal or gastric varices); any underlying condition that would contraindicate randomisation to oestrogen; having taken any form of systemic HRT in the 6 months preceding study entry	Comparable	Only clinical fractures were reported, as adverse events	Mean *T*-score at baseline approximately –2.5
Caniggia, 1984[53]	Healthy ambulatory women aged 54–74 years with symptomatic postmenopausal osteoporosis (marked radiolucency of the spine plus at least one crush fracture occurring spontaneously or after minimal trauma)	Overt vitamin D deficiency; malabsorption; treatment with adrenocortical steroids for ≥3 months in the past 5 years, or with anticonvulsants, oestrogens, gestogens, androgens, anabolic drugs, thiazide diuretics, sodium fluoride, calcium and vitamin D during the past 6 months	Data relating to the comparability of the groups at baseline is provided only in relation to biochemical parameters; these show some variations between groups	None given	–

continued

TABLE 183 *Studies of oestrogen in women with osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Ishida, 2001[118]	Postmenopausal women with established osteoporosis	Not given	No details	Not stated	Published as an abstract only
Lindsay, 1990[65]	Women presenting to a metabolic bone disease clinic with classic postmenopausal osteoporosis (low vertebral bone mass plus atraumatic vertebral crush fractures or vertebral deformities)	Secondary causes of bone loss; other significant medical conditions; contraindications to the use of oestrogens	Data are only presented for the 40 study completers; for these, both groups were comparable at baseline	NA	–
Lufkin, 1992[173]	Ambulatory postmenopausal white women with established type I osteoporosis	Evidence of any associated disease or history of use of any drug known to cause osteoporosis or to affect calcium levels; having taken fluoride or bisphosphonates; having taken calcium (>500 mg per day) in the previous 3 months or oestrogen or vitamin D in the previous 6 months	Comparable	Decrease of >15% in the anterior, middle or posterior vertebral height relative to baseline	The extent to which the study can be regarded as blinded is questionable, given that all 19 women with intact uteri in the HRT group experienced menstrual bleeding, whereas none of the 25 such women in the placebo group did
Pacifici, 1988[122]	White women with at least one non-traumatic vertebral fracture and/or evidence of spinal demineralisation by quantitative computer tomography	Conditions known to influence calcium metabolism; contraindications to the study medications	Baseline characteristics were not presented in relation to the 35 women who dropped out during the first year of the study, and there is no information regarding the comparability of all groups at entry	Compression fractures: a loss of posterior height >15% compared with the mean of the posterior height of the nearest (above and below) intact vertebrae. Wedging and biconcave fractures: a loss of anterior and central height >20% compared with the posterior height of the same vertebra	–

continued

TABLE 183 *Studies of oestrogen in women with osteoporosis or osteopenia: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Recker, 1999[72]	Healthy white women >65 years with a spinal BMD of ⩽0.90 g cm^{-2} (*T*-score ⩽–1.336)	Previous hip fracture; treatment with oestrogen or calcitonin in the previous 6 months; any treatment with bisphosphonates or fluoride; treatment for >6 months with corticosteroids; any corticosteroid treatment in the previous 6 months; endometrial thickness >6 mm as measured by transvaginal ultrasound; history of breast cancer; smoking more than 10 cigarettes per day	Comparable	That used by Davies *et al.*, 1993[175]	–
Wimalawansa, 1998[125]	Postmenopausal women with at least one but no more than four atraumatic thoracic vertebral crush fractures and spinal *T*-score <–2	Surgical menopause; secondary osteoporosis or other medical conditions that can affect the skeleton; medications that affect calcium metabolism within the previous 3 years; taking HRT, anabolic steroids, glucocorticoids, calcitonin, fluoride or bisphosphonates at any time since the menopause	Comparable	A reduction of ⩾20% in anterior, middle or posterior vertebral height plus a reduction of 15% or more in area in a previously unaffected vertebra. Further deterioration in the height or area of a previously affected vertebra was not considered a new fracture	–
Zarcone, 1997[174]	Women aged 45–63 years, naturally or surgically menopausal for ⩾4 years, with lumbar spine BMD ⩽0.88 g cm^{-2}	None stated	No demographic details are given, and the comparability of the groups is not discussed	None given	–

TABLE 184 *Studies of oestrogen in women with osteoporosis or osteopenia: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Alexandersen, 1999[50]	3	3	2	3	1	3	15/18 (83)	Rx1: 26 Rx2: 25 Rx3: 25 C: 24	Rx1: 65% Rx2: 68% Rx3: 60% C: 79%	Pharmaceutical company
Bone, 2000[52]	3	1	3	3	1	0	11/15 (73)	Rx1: 92 Rx 2: 143 Rx 3: 140 C: 50	Rx1: 74% Rx2: 76% Rx3: 79% C: 68%	Pharmaceutical company
Caniggia, 1984[53]	1	1	1	1	0	1	5/15 (33)	Rx1: 7 Rx2: 7 Rx3: 7 C: 7	Rx1: 71% Rx2: 71% Rx3: 100% C: 71%	Not specified
Ishida, 2001[118]	1	1	1	1	3	1	8/18 (44)	Total = 183	Not stated	Not specified
Lindsay, 1990[65]	1	1	2	3	1	0	8/15 (53)	Rx: 22 C: 18	Rx: 86% C: 61%	Government agency
Lufkin, 1992[173]	1	1	3	3	0	3	11/15 (73)	Rx: 36 C: 39	Rx: 92% C: 87%	Pharmaceutical company
Pacifici, 1988[122]	1	1	2	1	0	3	8/15 (53)	128	55% overall	Not stated
Recker, 1999[72]	3	1	3	3	0	3	13/15 (87)	Rx: 64 C: 64	Rx: 72% C: 81%	Government agency; pharmaceutical companies (medications only)
Wimalawansa, 1998[125]	2	3	2	3	1	3	14/18 (78)	Rx1: 18 Rx2: 17 Rx3: 19 C: 18	Rx1: 83% Rx2: 82% Rx3: 79% C: 78%	Not stated
Zarcone, 1997[174]	1	1	2	1	1	1	7/18 (39)	132	91% overall	Not stated

TABLE 185 *Studies of oestrogen in women with normal or unspecified BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Aitken, 1973[49]	Scotland	Not clear	Metacarpal mineral changes	Healthy women who had undergone hysterectomy and bilateral oophorectomy for non-malignant disease	48.9	Mestranol 40 μg per day	Placebo
Bjarnason, 2000[177]	Denmark	3 years	BMD	Healthy women within 1–6 years after the menopause, with an intact uterus	53.5 (48–60)	1 or 2 mg per day 17β-estradiol sequentially combined with 25 or 50 μg gestodene on days 17–28 of a 28-day cycle, in the following combinations: Rx1: 1/25 Rx2: 2/25 Rx3: 2/50 Rx4: 1 mg per day 17β-estradiol continuously combined with 25 μg per day gestodene	Placebo
Cauley, 2001[178]	USA	3 years	Non-fatal MI or CHD death	Postmenopausal women with documented coronary heart disease who had not had a hysterectomy	67±7[a] (44–79)	0.625 mg per day CEE plus medroxyprogesterone acetate 2.5 mg per day	Placebo
Cheng, 2000[85]	Finland	1 year	Bone/muscle ratio	Postmenopausal women	(50–57)	Rx1: HRT (combined estradionoretisteron acetate) Rx2: HRT plus exercise	Exercise
Delmas, 2000[55]	France	2 years	BMD	Postmenopausal women with a lumbar spine *T*-score between –2 and +2, and without osteoporotic fractures	58 (45–65)	Rx1: 1 mg per day 17β-estradiol + 0.25 mg per day NETA Rx2: 1 mg per day 17β-estradiol + 0.5 mg per day NETA	Placebo

continued

TABLE 185 *Studies of oestrogen in women with normal or unspecified BMD: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Eiken, 1997[57]	Denmark	8 years	Lumbar spine BMD	Normal early postmenopausal women without osteoporotic fracture	Not stated	Rx1: Continuous HRT (2 mg per day estradiol plus 1 mg per day NETA) (Kliogest) Rx2: sequential HRT (2 mg per day estradiol for 12 days, followed by 2 mg per day estradiol plus 1 mg per day NETA for 10 days, followed by 1 mg per day estradiol for 6 days) (Trisekvens)	Placebo
EPIC study[71]	USA, Europe	6 years	BMD	Healthy postmenopausal women, no more than 10% of whom had a lumbar spine BMD <0.8 g cm^{-2}	53.3 (45–59)	Rx1: 2.5 mg per day oral alendronate for 6 years Rx2: 2.5 mg per day oral alendronate for 4 years followed by placebo for 2 years Rx3: 2.5 mg per day oral alendronate for 2 years followed by placebo for 2 years Rx4: 5 mg per day oral alendronate for 6 years Rx5: 5 mg per day oral alendronate for 4 years followed by placebo for 2 years Rx6: 5 mg per day oral alendronate for 2 years followed by placebo for 4 years Rx7: open-label oestrogen–progestin (in USA, 0.625 mg per day CEE + 5 mg per day MPA; in Europe, 2 mg per day 17β-estradiol for 22 days, 1 mg per day NETA on days 13–22, and 1 mg per day estradiol on days 23–28) for 4 years Rx8: placebo for 4 years followed by 5 mg per day oral alendronate for 2 years	Placebo

continued

TABLE 185 *Studies of oestrogen in women with normal or unspecified BMD: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Gallagher, 2001[58]	USA	3 years	BMD	Elderly women with normal (±2 SD) *Z*-score at femoral neck	71±4[a] (65–77)	Rx1: HRT (0.625 mg per day CEE plus, in non-hysterectomised women, 2.5 mg per day MPA) Rx2: 0.25 µg b.d. calcitriol Rx3: HRT plus calcitriol	Placebo
Genant, 1997[59]	USA	2 years	BMD	Non-smoking, postmenopausal women with lumbar spine BMD within 2.0 SD of peak bone mass	51.5	0.3, 0.625 or 1.25 mg per day continuous esterified oestrogens	Placebo
Herrington, 2000[88]	USA	3 years	Mean minimum coronary artery diameter	Postmenopausal women with angiographically verified coronary artery disease	65.8	Rx1: 0.625 mg per day unopposed CEE Rx2: 0.625 mg per day plus 2.5 mg per day MPA	Placebo
Komulainen, 1995[162]	Scandinavia	5 years	BMD	Non-osteoporotic early postmenopausal women	52.7	Rx1: HRT (2 mg estradiol valerate on days 1–21, 1 mg cyproterone acetate on days 12–21) Rx2: vitamin D_3 [cholecaldiferol 300 IU per day (7.5 µg) per day] plus 93 mg per day Ca^{2+}; no intake during June–August; in this group, during the 5th year, the vitamin D_3 dose was reduced to 100 IU per day because of observed adverse lipid changes during vitamin D_3 treatment Rx3: HRT + calcium and vitamin D_3	500 mg per day calcium lactate (equivalent to 93 mg per day Ca^{2+})

continued

TABLE 185 *Studies of oestrogen in women with normal or unspecified BMD: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Lees, 2001[64]	UK, Canada	2 years	BMD	Non-hysterectomised postmenopausal women	55.6 ± 4.6[a] (44–65)	1 or 2 mg cyclical 17β-estradiol on days 1–28 and 5, 10 or 20 mg dydrogesterone on days 15–28 in the following combinations: Rx1: 1/5 Rx2: 1/10 Rx3: 2/10 Rx4: 2/20	Placebo
Mosekilde, 2000[179]	Denmark	20 years	Any osteoporotic fracture (vertebra, hip, humerus or wrist)	Postmenopausal women without non-traumatic vertebral fractures	49.8 (45–58)	Oral sequential HRT (1 mg per day estradiol on days 1–6, 2 mg per day on days 7–28, plus 1 mg per day Norethisteron on days 19–28) or, for hysterectomised women, 2 mg per day estradiol continuously Alternative formulations (detailed) were available for women suffering side-effects	No treatment
Mulnard, 2000[89]	USA	1 year	Cognition, mood	Hysterectomised women with mild to moderate Alzheimer's disease	75.1 (>60)	Rx1: CEE 0.625 mg per day CEE Rx2: 1.25 mg per day CEE	Placebo
Nachtigall, 1979[90]	USA	10 years	BMD	Postmenopausal women who were less physically active than the general population	Not stated	2.5 mg per day conjugated oestrogen plus 10 mg per day cyclic MPA for 7 days per month	Placebo
Orr-Walker, 2000[69]	New Zealand	2 years	BMD	Postmenopausal women with mild primary hyperparathyroidism	66.4	0.625 mg per day CEE plus, for non-hysterectomised women, 5 mg per day MPA	Placebo

continued

TABLE 185 *Studies of oestrogen in women with normal or unspecified BMD: general information (cont'd)*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
PEPI trial[91]	USA	3 years	CHD risk factors	Healthy postmenopausal women without a history of non-traumatic hip or spinal fracture	56.1 (45–64)	Rx1: 0.625 mg per day CEE Rx2: 0.625 mg per day CEE plus 10 mg per day MPA for 12 days per month Rx3: 0.625 mg per day CEE plus 2.5 mg per day MPA Rx4: 0.625 mg per day CEE plus 200 mg per day micronised progesterone for 12 days per month	Placebo
Voss, 2002[47]	Europe, Israel, South Africa	6 months	Uterine bleeding patterns; endometrial thickness; uterine volume	Healthy ambulatory women at least 2 years after their natural menopause	56.1 (⩽60)	Continuous combined HRT (2 mg per day oestradiol + 1 mg per day NETA) + placebo raloxifene	60 mg per day raloxifene + placebo HRT
Weiss, 1999[75]	USA	2 years	Lumbar BMD	Women who had undergone hysterectomy (if they had not undergone oophorectomies, ⩾45 years of age and with ovarian failure for at least 1 year)	51.2 (⩾40)	Transdermal estradiol: Rx1: 0.025 mg per day Rx2: 0.05 mg per day Rx3: 0.06 mg per day Rx4: 0.10 mg per day	Placebo
WHI trial[180]	USA	5 years	Non-fatal MI and CHD death	Postmenopausal women with an intact uterus at baseline	63.3 (50–79)	0.625 mg per day CEE plus 2.5 mg per day MPA	Placebo

[a] Mean ± SD.
MI, myocardial infarction.

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Aitken, 1973[49]	Healthy women who had undergone hysterectomy and bilateral oophorectomy for non-malignant disease 2 months, 3 years or 6 years previously	History of hepatitis, DVT or pulmonary embolism; specific diseases known to be associated with bone mineral loss; use of HRT between oophorectomy and study recruitment	Groups said to be comparable in terms of mean age and standardised metacarpal ash; no other information provided	NA	The length of this study is not clear; it is not stated to have been randomised, but this is implicit in the double-blinding
Bjarnason, 2000[177]	Healthy women with an intact uterus within 1–6 years after menopause	Taking medication known to affect calcium metabolism; clinical or laboratory evidence of confounding diseases; history of stroke; MI within previous 6 months or requiring permanent medication to control cardiac disease; thromboembolic disorders either unrelated to oestrogen in the past 3 years or related to oestrogen ever; taking HRT within previous 3 months	Baseline data only provided for the 153 study completers; these were comparable in the five groups	NA	–
Cauley, 2001[178]	Postmenopausal women age <80 years with documented coronary disease (MI, coronary artery bypass surgery, percutaneous coronary revascularisation, or angiographic evidence of at least 50% narrowing of one or more major coronary arteries). About 12% in the treatment arm and 17% in the placebo arm were osteoporotic ($p = 0.13$)	Hysterectomy; coronary event within the 6 months preceding randomisation; serum triglycerides $\geq$300 mg dl^{-1}; having used hormones within 3 months; history of DVT, pulmonary embolism, breast or endometrial cancer, uncontrolled hypertension or diabetes; other life-threatening diseases	Comparable	NA	–
Cheng, 2000[85]	Healthy women aged 50–57 years, <5 years after onset of the menopause	Previous HRT use	No data	NA	Study published as an abstract only

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Delmas, 2000[55]	Healthy postmenopausal women aged 45–65 years with a lumbar spine *T*-score between –2 and +2. Postmenopausal status was defined as cessation of menstrual bleeding for ⩾1 year, estradiol levels ⩽30 pg ml^{-1} and FSH levels >40 IU l^{-1}	Endometrial thickness >4 mm; known or suspected past history of breast cancer or oestrogen-dependent cancer; liver diseases; active or past history of venous thromboembolism; thromboembolic disorders or cerebrovascular accidents; abnormal vaginal bleeding of unknown aetiology; pituitary tumour; diabetes mellitus; unstable thyroid diseases; congestive heart failure, angina pectoris, arrhythmia, MI; systolic blood pressure >170 mmHg and/or diastolic blood pressure >100 mmHg; renal failure; oestrogen/progestogen treatment within the previous 6 months; calcitonin treatment with washout of <6 months; fluoride treatment for >6 months, or for <6 months and washout of <6 months; more than two courses of bisphosphonate treatment and/or washout of <6 months; osteoporotic (i.e. non-traumatic vertebral crush) fractures; Paget's disease of bone; primary hyperparathyroidism; osteomalacia; known lumbar arthrosis with or without lumbar scoliosis; porphyria; current liver enzyme inducing medication; known alcohol or drug abuse; heavy tobacco consumption; participation in other studies involving other investigational products within the previous 3 months	Comparable	NA	–
Eiken, 1997[57]	Women living in the hospital catchment area and born between 1930 and 1933 with last vaginal bleeding >6 and <24 months earlier	Previous or current malignant disease; thromboembolic disease; parenchymatous liver disease; chronic pancreatitis; intestinal malabsorption; diabetes mellitus; obesity; low energy fracture; diseases with high or low turnover of bone; treatment with oestrogen, progesterone, corticosteroids, fluoride, vitamin D or drugs known to provoke induction of liver enzymes	No baseline data available other than lumbar and forearm BMD, which are comparable	NA	–

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
EPIC study[71]	Women aged 65–77 years with normal femoral neck BMD (*Z*-score 2.0 to –2.0)	Severe chronic illness; primary hyperparathyroidism; active renal stone disease; had taken bisphosphonates, anticonvulsants, oestrogen, fluoride or thiazide diuretics in the previous 6 months	Comparable	Not given	The mean *T*-score at baseline was approximately –2.5
Gallagher, 2001[58]	Naturally or surgically menopausal women (final menstrual period or oophorectomy >6 and <4 years earlier; FSH levels <50 IU l^{-1}) with baseline lumbar BMD *T*-score –2 to +2	Taking oestrogen replacement therapy or HRT within 8 weeks of beginning study medication; taking drugs that affect bone mineral metabolism (e.g. bisphosphonates, calcitonin or androgen)	Comparable	NA	–
Genant, 1997[59]	Postmenopausal women not currently receiving oestrogen replacement therapy, and with one or more epicardial coronary stenoses of at least 30% of the luminal diameter, as measured by quantitative coronary angiography	Known or suspected breast or endometrial carcinoma; previous or planned coronary artery bypass surgery; history of DVT or pulmonary embolism; symptomatic gallstones; serum aspartate aminotransferase level >1.5 times normal; triglyceride level >400 mg dl^{-1}; >70% stenosis of the left main coronary artery; uncontrolled hypertension; uncontrolled diabetes	Comparable in terms of demographic characteristics and CHD risk factors and manifestations, but with a non-significant trend towards more severe disease in those women assigned to combined therapy. No information regarding comparability in terms of BMD or fracture history	Not given	Side-effects such as vaginal bleeding, especially in the group receiving unopposed oestrogen, produced differential rates of compliance and opportunities for unblinding
Herrington, 2000[88]	Postmenopausal women (>6 and <24 months since last menstruation)	Contraindications for HRT; history of breast or endometrial cancer, thromboembolic diseases or medication-resistant hypertension	Comparable	NA	–
Komulainen, 1998[162]			Comparable	NA	–

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Lees, 2001[64]	Non-osteoporotic, non-hysterectomised women aged between 44 and 65 years, naturally postmenopausal (amenorrhoea for >6 months), with BMD in the lumbar spine and femoral neck at least 0.80 and 0.65 g cm^{-2} (Lunar), respectively (0.70 and 0.52 g cm^{-2} Hologic)	Endometrial hyperplasia or neoplasia; had ever used HRT by implant or other types of HRT in the previous 6 months; had ever used bisphosphonates or fluoride; evidence of cancer, renal, liver or cardiovascular disease, hypertension or diabetes; >25% heavier than ideal body weight; evidence of alcohol or drug misuse	Comparable	NA	–
Mosekilde, 2000[179]	Women aged 45–58 years with an intact uterus and 3–24 months past last menstrual bleeding, or experiencing perimenopausal symptoms (including irregular menstruation) plus elevated FSH; or hysterectomised women aged 45–52 years with elevated FSH	Metabolic bone disease, including osteoporosis defined as non-traumatic vertebral fractures on X-ray; current oestrogen use or oestrogen use within the past 3 months; current or past treatment with glucocorticoids for >6 months; current or past malignancy; newly diagnosed or uncontrolled chronic disease; alcohol or drug addiction	In the randomised part of the study, the control group was slightly, but statistically significantly, older than the HRT group, and had slightly but statistically significantly lower BMD at lumbar spine and ultradistal forearm; the groups were similar in other respects	NA	–

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Mulnard, 2000[89]	Hysterectomised women aged >60 years with a diagnosis of probable Alzheimer's disease in the mild to moderate stage (Mini-Mental State Examination score 12–28)	Major clinical depressive disorder (score of <17 on the Hamilton Depression Rating Scale); abnormal gynaecological, breast and mammography examination results; MI within 1 year; history of thromboembolic disease or hypercoagulable state; hyperlipidaemia; use of oestrogens within 3 months; current use of antipsychotics, anticonvulsants, anticoagulants, β-blockers, narcotics, methyldopa, clonidine or prescription cognition-enhancing or antiparkinson medications	No baseline data available other than bone mass	Not given	The study was carried out in hysterectomised women to allow the use of unopposed oestrogens, because of some evidence that progesterone may mitigate some of oestrogen's beneficial effects in the CNS. However, episodes of vaginal bleeding indicated that four women had not been hysterectomised, despite confirmatory gynaecological examination before randomisation
Nachtigall, 1979[90]	Patients at a hospital for chronic diseases	Concurrent systemic illness; untreated thyroid disease; hepatic or renal dysfunction; undiagnosed genital bleeding; oestrogen therapy within the past 6 months; any history of bisphosphonate or fluoride therapy; current use of a glucocorticoid drug, an anticonvulsant agent or a thiazide diuretic	Baseline data provided only relating to those women who completed the first 2 years of the study; they were comparable in terms of age, body mass index (BMI), BMD, time since menopause, calcium and alcohol intakes. Of those who continued in the study at 2 years, the HRT group had lower BMD at several sites than the placebo group	Reductions in anterior, middle or posterior heights that were $\geq$20% and $\geq$4 mm	Details of the randomisation process are unclear: it seems that women were matched in pairs for age and disease and then each pair was randomised to treatment allocation. If this is so, the study cannot be described as truly randomised

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Orr-Walker, 2000[69]	Postmenopausal women with mild primary hyperparathyroidism	Not taking oestrogens or progestins for ⩾2 before the first screening visit (4 months before randomisation); extreme hyperlipidaemia; marked obesity; severe hypertension; recent MI; congestive heart failure; stroke (or transient ischaemic attack); antiarrhythmia medication use; insulin-dependent diabetes mellitus; prior breast or endometrial cancer; melanoma; any non-basal cell skin cancer in the previous 5 years; an elevated, highly sensitive, thyroid-stimulating hormone concentration; history of trauma to the lower spine or hip fracture; chronic steroid use; severe menopausal symptoms	Comparable	NA	Because vaginal bleeding reliably indicated the use of HRT, some women may have learned of their study allocation despite double-blinding. However, the authors suggest that this is unlikely to have influenced the conduct of the study, as compliance and withdrawal rates were comparable in both groups, and BMD and biochemical variables were measured by people who were unaware of the occurrence of vaginal bleeding
PEPI trial[91]	Women aged 45–64 years who were surgically or naturally postmenopausal (>1 but <10 years since last menstrual period) and, if treated with thyroid hormone replacement, to have been on a stable dose for ⩾3 months before initial screening	Known or suspected bone disease; hypocalcaemia or hypercalcaemia; vitamin D deficiency; bone fracture within previous 6 months; immobilisation for ⩾2 of the preceding 6 months; hot flushes requiring hormone therapy; history of skin irritation caused by transdermal drug-delivery systems; had ever taken bisphosphonates, fluoride or calcitonin; receiving chronic treatment with corticosteroids or agents that affect bone metabolism; had recent oestrogen replacement therapy or treatment with lipid-lowering drugs; had participated in another clinical trial within 3 months	Comparable	NA	–

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Voss, 2002[47]	Healthy ambulatory women aged ≤60 years, ≥2 years after their natural menopause	History of hysterectomy, ovariectomy, breast cancer or oestrogen-dependent cancer; any other cancer within the past 5 years; DVT or thromboembolism; liver disease; significant hypothyroidism or hyperthyroidism; not qualifying for therapy according to the prescribing information for E2 and NETA; endometrial thickness of >5 mm or any clinically significant endometrial or ovarian pathology; suspicious mammographic findings; severe postmenopausal symptoms requiring HRT use; treated with oestrogens/progestins in the past 6 months or hypolipidaemic drugs in the past 3 months	Comparable	NA	–
Weiss, 1999[75]	Hysterectomised women (if not oophorectomised, ≥45 years old and with ovarian failure as evidenced by vasomotor symptoms for ≥1–5 years before enrolment; if oophorectomised, ≥40 years old, and 4 weeks to 5 years post-oophorectomy), with baseline lumbar BMD ≥0.09 g cm^{-2} (Lunar) or 0.086 g cm^{-2} (Hologic)	Any medical condition likely to be associated with a predicted survival of <3 years; prior breast cancer; other prior cancer within the past 10 years (except for non-melanoma skin cancer); low haematocrit or platelet counts; alcoholism; dementia	Groups similar in age, weight and ethnic mix. Information on other relevant factors (e.g. baseline BMD, smoking) not given	Clinical only	The finalised analyses of this study have yet to be published. The relatively high rates of discontinuation in the treatment arm and cross-over to active treatment in the placebo arm will tend to decrease any observed treatment effects, both adverse and beneficial

continued

TABLE 186 *Studies of oestrogen in women with normal or unspecified BMD: inclusion and exclusion criteria (cont'd)*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
WHI trial[180]	Women aged 50–79 years, postmenopausal (no vaginal bleeding for 6 months, or 12 months for 50–54-year-olds; or hysterectomised, or having ever used postmenopausal hormones), likely to reside in the area for 3 years	Any medical condition likely to be associated with a predicted survival of <3 years; prior breast cancer; other prior cancer (except for non-melanoma skin cancer) in the past 10 years; low haematocrit or platelet counts; adherence and retention concerns (e.g. alcoholism, dementia)	Comparable	Clinical only	The original study design allowed randomisation to unopposed oestrogen, oestrogen plus progestin, or placebo. When it was demonstrated that long-term unopposed oestrogen was inappropriate for women with a uterus, the protocol was changed to randomisation to either oestrogen plus progestin or placebo. 331 women who had been assigned to unopposed oestrogen were unblinded and reassigned to oestrogen plus progestin. Considerable effort was made to maintain blinding of other participants and clinic staff. Some flexibility of doses of oestrogen and progestin was allowed to manage symptoms such as breast tenderness and vaginal bleeding. Women who had a hysterectomy during the study were switched to unopposed oestrogen or placebo without unblinding; they were included in the original randomisation group for analyses

FSH, follicle-stimulating hormone.

TABLE 187 *Studies of oestrogen in women with normal or unspecified BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Aitken, 1973[49]	1	1	2	1	1	0	6/15 (40)	Rx: 84 C: 81 + 2 subjects not attributed to treatment groups	78% overall completed at least 1 year	Not specified
Bjarnason, 2000[177]	1	1	1	1	1	1	6/18 (33)	Rx1: 56 Rx2: 55 Rx3: 56 Rx4: 56 C: 56	Rx1: 54% Rx2: 24% Rx3: 46% Rx4: 58% C: 73%	Pharmaceutical company
Cauley, 2001[178]	3	3	3	3	3	0	15/15 (100)	Rx: 1380 C: 1383	Rx: 64% C: 71%	Pharmaceutical company
Cheng, 2000[85]	1	1	1	1	1	0	5/15 (33)	80	No data	Not stated
Delmas, 2000[55]	1	3	3	3	1	0	11/15 (73)	Rx1: 44 Rx2: 46 C: 45	Rx1: 70% Rx2: 63% C: 73%	Pharmaceutical company
Eiken, 1997[57]	1	1	1	1	1	0	5/15 (33)	Rx1: 50 Rx2: 50 C: 51	Rx: 48% C: 51%	Pharmaceutical company
EPIC study[71]	1	NA	3	3	1	0	8/12 (67)	Rx1: 165 Rx2: 165 Rx3: 169 Rx4: 168 Rx5: 165 Rx6: 165 Rx7: 110 Rx8: 250 C: 252	Rx1: 50% Rx2: 58% Rx3: 77%[a] Rx4: 54% Rx5: 52% Rx6: 57% Rx7: 25%[a] Rx8: 47% C: 52%	Pharmaceutical company

continued

TABLE 187 *Studies of oestrogen in women with normal or unspecified BMD: methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Gallagher, 2001[58]	1	3	3	2	3	3	15/18 (83)	Rx1: 123 Rx2: 121 Rx3: 122 C: 123	Rx1: 82% Rx2: 83% Rx3: 84% C: 91%	Government agency (main funder); pharmaceutical companies
Genant, 1997[59]	1	3	2	3	1	0	10/15 (67)	Rx1: 101 Rx2: 102 Rx3: 100 C: 103	Rx1: 65% Rx2: 53% Rx3: 36% C: 60%	Pharmaceutical company
Herrington, 2000[88]	1	3	3	3	1	1	12/18 (67)	Rx1: 100 Rx2: 104 C: 105	Not clear	National institute (main funder); pharmaceutical company
Komulainen, 1998[162]	3	3	3	3	3	0	15/15 (100)	Rx1: 116 Rx2: 116 Rx3: 116 C: 116	Rx1: 64% Rx2: 89% Rx3: 74% C: 91%	Pharmaceutical companies
Lees, 2001[64]	1	1	2	3	1	0	8/15 (53)	Rx1: 117 Rx2: 114 Rx3: 117 Rx4: 118 C: 113	62% overall	Health trust; pharmaceutical company
Mosekilde, 2000[179]	2	3	3	2	3	3	16/18 (89)	Rx: 502 C: 504	Rx: 89% C: 89%	Private foundation (unspecified); local government; pharmaceutical companies

continued

TABLE 187 *Studies of oestrogen in women with normal or unspecified BMD: methodological quality (cont'd)*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Mulnard, 2000[89]	3	1	3	3	1	0	11/15 (73)	Rx1: 42 Rx2: 39 C: 39	Rx1: 83% Rx2: 77% C: 82%	National institute (main funder); pharmaceutical company
Nachtigall, 1979[90]	1	1	1	3	1	0	7/15 (47)	Rx: 84 C: 84	Not clear	Not specified
Orr-Walker, 2000[69]	3	3	2	3	0	3	14/15 (93)	Rx: 21 C: 21	Rx: 52% C: 57%	Local and national research bodies; national lottery
PEPI trial[91]	3	3	3	3	1	0	13/15 (87)	Rx1: 175 Rx2: 174 Rx3: 174 Rx4: 178 C: 174	Not stated	National institutes (main funders); pharmaceutical companies
Voss, 2002[47]	3	3[b]	3	3	0	0	12/12 (100)	Rx1: 513 Rx2: 495	Rx1: 77% Rx2: 89%	Pharmaceutical company
Weiss, 1999[75]	3	3	3	3	1	0	13/15 (87)	Rx1: 32 Rx2: 31 Rx3: 31 Rx4: 35 C: 46	55% overall	Pharmaceutical company
WHI trial[180]	3	3	3	3	3	0	15/15 (100)	Rx: 8506 C: 8102	Rx: 58% C: 62%	National institute (main funder); pharmaceutical company

[a] At 4 years.
[b] Assessors of endometrial/uterine end-points.

TABLE 188 *Oestrogen: toxicity*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Aitken, 1973[49]	Only one side-effect was said to be relatively common (unquantified) in the treatment group: cramps in the calves and feet when in bed at night. Three further 'vascular' complications were seen in the treatment group (recurrence of superficial phlebitis, an episode of palpitation and chest pain, and a transient hemiparesis)	–	Not reported
Alexandersen, 1999[50]	Endometrial bleeding occurred in six women (23%) in the HRT group, five (20%) in the HRT/MFP group, two (8%) in the MFP group and two (8%) in the placebo group. Breast tenderness, weight gain, mood change and nausea occurred in 17 women (65%) in the HRT group, 19 (76%) in the HRT/MFP group, ten (40%) in the MFP group and three (13%) in the placebo group; in almost all cases, the severity was mild or moderate	Four women (15%) in the HRT group and seven (27–28%) in each of the other groups reported adverse events of interest in relation to MFP (joint pain, pain in the extremities and heartburn); in all cases the severity was mild or moderate	There were nine dropouts because of breast tenderness, oedema, headache, nausea, weight gain and mood change: two each (8%) in the HRT and MFP groups, four (16%) in the HRT/MFP group and one (4%) in the placebo group. Other withdrawals because of adverse events were as follows: leg pain (one in placebo group), erythema (patch) (one in placebo group and one in MFP group), endometrial bleeding (one in HRT/MFP)
Bjarnason, 2000[177]	HRT-related adverse events included vaginal bleeding and breast tenderness: the former was less problematic in the continuous treatment group, and the latter occurred with equal frequency in all HRT groups. Three possible HRT-related serious adverse events occurred during the study: breast cancer in two women receiving sequential HRT (1/25) after 2 years of treatment, and uterine cancer in one woman receiving continuous HRT after 2 years of treatment	–	The number of withdrawals was said to be significantly higher than from the placebo group from all HRT groups except the continuous treatment group. Discontinuation because of vaginal bleeding was significantly more frequent in the HRT groups than in the placebo group ($p < 0.001$). A trend towards a higher withdrawal rate for vaginal bleeding in the high-dose compared with the low-dose HRT groups was not statistically significant. Data relating to other discontinuations because of adverse events were not provided
Bone, 2000[52]	Oestrogen, alone or in combination with alendronate, was frequently associated with complaints such as breast pain and weight gain	Upper GI adverse events occurred in 27% of women receiving alendronate, 30% receiving oestrogen, 34% receiving combination therapy and 22% in the placebo group (no significant difference between treatment groups)	Alendronate: 6% Oestrogen: 10% Combination therapy: 9% Placebo: 10%

continued

TABLE 188 *Oestrogen: toxicity (cont'd)*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Caniggia, 1984[53]	None reported	None reported	Not specified
Cauley, 2001[178]	Venous thromboembolic events were three times more common in the hormone group than in the placebo group (RH 2.89, 95% CI 1.50 to 5.58). There was also an increased risk of gallbladder disease in the hormone group (RH 1.38, 95% CI 1.00 to 1.92)	–	No data
Cheng, 2000[85]	None reported	None reported	None reported
Delmas, 2000[55]	HRT-related adverse events included vaginal bleeding and breast tenderness. The highest incidence of bleeding in the treatment groups was reported during the first 3 months, when 28–29% of women reported at least 1 day of bleeding every month	–	30 withdrawals were due to adverse events (11 in the NETA 0.25 mg group, 13 in the NETA 0.5 mg group and six in the placebo group). The most common adverse events that led to withdrawal from the treatment groups were breast pain and bleeding: these accounted for six and three of the withdrawals from the NETA 0.25 mg and 0.5 mg groups, respectively. Two of the discontinuations due to adverse events in the placebo group were reported to be due to vertebral fractures
Eiken, 1997[57]	None reported	None reported	Not specified
EPIC study[71]	The most commonly reported adverse events in the oestrogen–progestin group were withdrawal bleeding and breast tenderness	At 4 years, drug-related adverse events (including upper GI adverse events) had occurred in 11% of women in the 5 mg group, 16% in the 5 mg/placebo group, 15% in the 2.5 mg group and 9% in the 2.5 mg/placebo group, compared with 13% in the placebo group and 88% in the oestrogen–progestin group. The number of women suffering upper GI adverse events was similar in all groups, ranging between 37 and 46%	Number not specified. Withdrawal bleeding and breast tenderness did not lead to a higher rate of study withdrawal in the HRT group

continued

TABLE 188 *Oestrogen: toxicity (cont'd)*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Gallagher, 2001[58]	Eight women (3%) in the groups receiving oestrogen and three (1%) in the other groups had gallstones or cholecystitis. Four women (1.6%) in the oestrogen groups had DVT compared with one (0.4%) in the other groups		21 women discontinued medication because of bleeding problems, 13 because of breast tenderness, 15 because of cerebrovascular incident/cerebral thrombosis/cerebral haemorrhage/transient ischaemic attack, 14 because of GI problems and 21 because of other significant health problems. These were not attributed to study groups
Genant, 1997[59]	The incidence and severity of vaginal bleeding were similar in the placebo and 0.3 mg groups; significantly more bleeding was noted in the 0.625 and 1.25 mg groups. Endometrial hyperplasia was noted in 1.7% of the placebo and 0.3 mg groups, 28% of the 0.625 mg group ($p < 0.5$) and 53% of the 1.25 mg group ($p < 0.5$)		The most common adverse events that led to discontinuation of the study medication were headaches and vaginal bleeding; the incidence of these increased in a dose-related manner. 53 women (17%) withdrew from the oestrogen groups for endometrial-related reasons, compared with only three (3%) from the placebo group. Endometrial hyperplasia was a major reason for withdrawal only in the groups receiving 0.625 or 1.25 mg: 16% and 32% of those groups, respectively, withdrew for that reason. 49 women (12 from the placebo group, ten each from the 0.3 and 0.625 mg groups, and 17 from the 1.25 mg group) withdrew as a result of a variety of other adverse events
Herrington, 2000[88]	Five women assigned to unopposed oestrogen had venous thromboembolic events (clinically verified DVT or pulmonary embolism), compared with two assigned to combined therapy and one assigned to placebo ($p = 0.11$ for the comparison of unopposed oestrogen with placebo). Simple or complex hyperplasia was also more common in the group assigned to unopposed oestrogen ($p < 0.001$). The rates of cholecystectomy and of breast and other cancers were not significantly different among groups, but the incidence of these events was very low		Nine women died of CHD and 19 had non-fatal MIs during follow-up; there were no significant differences between the groups in the rate of these events
Ishida, 2001[118]	No data	No data	No data
Komulainen, 1998[162]	No data	Serious adverse events were evenly distributed between the four treatment groups[229]	There were more withdrawals from the HRT ($n = 42$) and HRT + vitamin D groups ($n = 30$) than from the vitamin D ($n = 13$) and placebo ($n = 11$) groups. The most common reasons for non-compliance were menstrual disorders ($n = 19$) or headache ($n = 14$); these were not attributed to groups

continued

TABLE 188 *Oestrogen: toxicity (cont'd)*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Lees, 2001[64]	Adverse events recorded with a frequency of more than 10% were those expected with HRT (breast pain, nausea, abdominal pain, dysmenorrhoea). Breast tenderness tended to occur more frequently in women receiving 2 mg estradiol than in those receiving 1 mg or placebo (36%, 24% and 12%, respectively)	No details	34 women (6%) withdrew owing to bleeding problems; these were fairly evenly distributed between the HRT groups. 83 women (14%) withdrew because of adverse events unrelated to bleeding problems: these were fairly evenly distributed between all groups, and the majority were not serious and not related to treatment
Lindsay, 1990[65]	No data	No data	No data
Lufkin, 1992[173]	All 19 women with intact uteri in the HRT group experienced menstrual bleeding, whereas none of the 25 such women in the placebo group did. Adverse events included skin irritation in four women (11%) in the HRT group and four (10%) in the placebo group, breast tenderness in 20 women (56%) in the HRT group and two (5%) in the placebo group, and endometrial hyperplasia in three women (8%) in the HRT group. Breast cancer was diagnosed shortly after study conclusion in two women, one from each group	–	Two women withdrew from the treatment group and one from the placebo group because of skin reaction to the patches
Mosekilde, 2000[179]	No data	No data	No data
Mulnard, 2000[89]	Treatment-related adverse events were not significantly different between the placebo and oestrogen groups. There were four episodes of DVT, two in the low-dose and two in the high-dose oestrogen groups	No data	No data
Nachtigall, 1979[90]	No data	–	No data

continued

TABLE 188 *Oestrogen: toxicity (cont'd)*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Orr-Walker, 2000[69]	14 out of 17 (83%) of women receiving HRT and six out of 16 (38%) of the placebo group suffered mastalgia ($p < 0.05$); one woman in the HRT group had her CEE dose reduced to 0.3 mg per day because of substantial mastalgia while receiving 0.625 mg per day. 53% of the HRT group, and none of the placebo group, suffered vaginal bleeding ($p < 0.001$). However, both of these events were mild and self-limiting; neither caused women to withdraw from the study	–	Nine women withdrew from the study during the 2-year period. Three withdrew from the HRT group for clinical reasons (mood disturbance $n = 1$, development of thyrotoxicosis $n = 1$, diffuse aching in the lower limbs $n = 1$), as did three from the placebo group (seronegative polyarticular arthritis $n = 1$, renal impairment $n = 1$, symptomatic hypercalcaemia requiring parathyroidectomy $n = 1$)
Pacifici, 1988[122]	Significant side-effects were said to occur only in the hormone group, and consisted primarily of pelvic congestion and cyclic bleeding; it is not stated how many women were affected	–	None
PEPI trial[91,187]	At 1 and 3 years, women in each active treatment group had significantly lower vasomotor symptom levels than those in the placebo group. Anxiety symptom levels were lower in CEE-adherent women than in those receiving placebo. Breast discomfort was significantly more common in women receiving combination treatment than in those receiving either placebo or unopposed oestrogens		210 (24%) women stopped treatment permanently: of these, 51 were protocol mandated (32 because of endometrial abnormalities), 127 because of symptoms, 11 because of concerns about health risks and 21 because of personal circumstances. The most frequently cited symptoms were vaginal bleeding ($n = 25$), premenstrual-like symptoms ($n = 11$), headaches ($n = 10$), anxiety/depression ($n = 10$) and breast tenderness ($n = 7$)
Recker, 1999[72]	Side-effects thought to be related to HRT were mild, short lived and easily tolerated by most patients; most disappeared within 6 months	–	Seven patients in the HRT group and two in the placebo group stopped taking the study medication but remained under observation for the full 3.5 years. All nine stopped because of symptoms thought to be related to HRT (breast tenderness, spotting, pelvic discomfort and mood changes)
Voss, 2002[47]	Women taking HRT were significantly more likely to have vaginal bleeding or spotting than those taking raloxifene (55% vs 7%, $p < 0.01$)		65 women (12.7%) withdrew from the HRT group and 24 (4.8%) from the raloxifene group as a result of adverse events ($p < 0.001$). Breast pain and vaginal bleeding were the main adverse events leading to withdrawal from the HRT group, causing withdrawal in 19 (3.7%) and nine women (1.8%) respectively

continued

TABLE 188 *Oestrogen: toxicity (cont'd)*

Study	HRT-related adverse events	Other adverse events	Withdrawals/discontinuation of study medication due to adverse events
Weiss, 1999[75]	No data	–	One withdrawal was due to vasomotor symptoms, and 20 to adverse events; these were not attributed to treatment groups
Wimalawansa, 1998[125]	None reported	23 women (32%) distributed through all the groups complained of minor side-effects attributable to calcium, but continued supplementation	HRT: 17% Etidronate: 12% Combination therapy: 21% Control: 17%
WHI trial[180]	There was a 26% increase in invasive breast cancer rates (166 women in the treatment group vs 124 in the placebo group), but a reduction of 37% in colorectal cancer rates (45 vs 67 women). Endometrial, lung and total cancer incidence were not affected	The rate of women experiencing CHD increased by 29% for women in the treatment group compared with the placebo group (164 vs 122 women). Stroke rates were also 41% higher in the treatment group (127 vs 85 women)	42% of the treatment group and 38% of the placebo group stopped taking study drugs at some time
Zarcone, 1997[174]	No data	–	12 women (9.1%) withdrew. It is not stated from which groups they came, and only one reason is given for all – "the common prejudices which associate the use of oestrogen replacement therapy with health risks"

MFP, monofluorophosphate.

TABLE 189 *Studies of exercise in women with osteoporosis: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention/dose	Comparison(s)
Bravo, 1996[198]	Canada	1 year	BMD	Postmenopausal women with low spinal BMD	59.8 (50–70)	Hour-long exercise classes three times a week	No treatment
Ebrahim, 1997[197]	UK	2 years	BMD	Postmenopausal women with established osteoporosis (upper limb fracture in past 2 years)	68.0	Brisk walking building to 40 minutes three times a week	Upper limb exercises
Winegard, 2001[199]	Canada	1 year	Quality of life measured by a disease-specific osteoporosis quality of life questionnaire	Elderly women with symptomatic osteoporosis-related vertebral fractures	74.4 (61–88)	Home exercise programme incorporating a tailored range of motion, strengthening and aerobic conditioning, performed for at least 60 minutes three times a week	No treatment

TABLE 190 *Studies of exercise in women with osteoporosis: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
Bravo, 1996[198]	Women aged 50–70 years who had been menopausal for ⩾12 months and who were osteopenic (lumbar BMD <1 g cm^{-2} or proximal femur BMD <0.9 g cm^{-2})	Institutionalised; expecting to be absent from the city for >2 months; contraindications to undertaking physical activities without close medical supervision	The groups were comparable at baseline in most respects, but time since menopause was longer in the control group, and the average psychological well-being of the control group was significantly lower than that of the treatment group. More women in the treatment group were taking progesterone, and slightly more were taking oestrogen and calcium. As these factors favoured the treatment group, they were controlled for in the analyses	NA	Randomisation was blocked and stratified by age (5-year groups) and by whether the subject was on cyclical etidronate therapy and/or oestrogen replacement therapy
Ebrahim, 1997[197]	Postmenopausal women who had sustained an upper arm fracture in the past 2 years	Current treatment for osteoporosis with bisphosphonates; expected survival of <1 year; cognitive impairment; too frail to withstand the brisk walking intervention or travel for measurements	The brisk walking group was slightly younger than the placebo group, but otherwise the groups were very similar	A 25% difference between anterior and posterior vertebral heights	–
Winegard, 2001[199]	Elderly women with symptomatic osteoporosis-related vertebral fractures	Not specified	No data provided relating to comparability	NA	Study available only as an abstract reporting interim results

TABLE 191 *Studies of exercise in women with osteoporosis: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
Bravo, 1996[198]	2	3	1	3	0	0	9/12	Rx: 70 C: 72	Rx: 63% C: not stated	National body
Ebrahim, 1997[197]	2	3	2	2	1	2	12/18 (67)	Rx: 81 C: 84	Rx: 60% C: 57%	Charitable trust
Winegard, 2001[199]	1	1	1	1	0	0	4/12 (33)	48 overall	No data	Not stated

TABLE 192 *Studies of exercise in postmenopausal women not selected for low BMD: general information*

Study	Study site	Length of study	Primary outcome measure(s)	Population	Mean age (range) (years)	Intervention	Comparison(s)
McMurdo, 1997[200]	UK	2 years	BMD	Women	64.5 (60–73)	Exercise class (45 minutes of weight-bearing exercise to music) three times a week for three 10-week terms a year + 1000 mg per day calcium	1000 mg per day calcium
Preisinger, 1995,[203] 2001[201]	Austria	Mean 3±1.3 years	BMD	Healthy Caucasian women, postmenopausal for at least 1 year	60.4 (45–75)	Exercise programme (warm-ups, stretching exercises and complex exercises designed to improve faulty posture, muscle strength, neuromotor control and coordination) to be performed for 20 minutes at least three times a week	No treatment
Sinaki, 2002[202]	USA	2 years, +	Vertebral fracture	Healthy, white, non-smoking, postmenopausal women	55.6 (48–65)	Intensive progressive weight-lifting exercise programme for the back extensor muscles	No treatment

TABLE 193 *Studies of exercise in younger postmenopausal women with normal to low BMD: inclusion and exclusion criteria*

Study	Inclusion criteria	Exclusion criteria	Baseline comparability	Vertebral fracture definition	Comments
McMurdo, 1997[200]	Elderly women	Conditions or drug treatments likely to affect bone	Comparable	NA	–
Preisinger, 1995,[203] 2001[201]	Healthy Caucasian women aged 45–75 years, postmenopausal for ⩾1 year, with regular physical activity below 5 metabolic equivalents (equivalent to walking at a speed of 5.6 km per hour)	Malabsorption; metabolic bone or chronic disease other than osteoporosis; smoking; alcohol abuse; secondary osteoporosis; drug therapy for osteoporosis other than oestrogens; taking steroid hormones, anticonvulsant drugs or thiazide diuretics; abnormal laboratory test results; functional inability to perform the exercise programme	The exercise group was older, and had lower BMD than, the control group	A reduction of ⩾20% from baseline in anterior, middle and/or posterior vertebral height over an area of >10%	–
Sinaki, 2002[202]	Healthy white non-smoking postmenopausal women	Recent history of back pain or back injury; radiographic evidence of vertebral wedging or compression; consuming special diets that affect bone metabolism or muscle mass; calcium, vitamin D or oestrogen supplementation; abnormal laboratory test results	The exercise group had greater back extensor strength and a higher physical activity score than the control group	A reduction of ⩾20% in anterior, middle or posterior vertebral height	At the end of the 2-year trial, the exercise group discontinued the prescribed exercises; all subjects were free to participate in any self-selected physical activities and were not monitored. Although a few subjects had received HRT during the intervening period, none had taken it for >4 months

TABLE 194 *Studies of exercise in younger postmenopausal women with normal to low BMD: methodological quality*

Study	Randomisation	Blinding of fracture outcome assessors	Handling of withdrawals	Comparability of groups at entry	Diagnosis of non-vertebral fracture	Diagnosis of vertebral fracture	Total methodology score (%)	No. of subjects randomised to study	% Completing study protocol	Source of funding
McMurdo, 1997[200]	1	1	1	3	1	0	7/15 (47)	Rx: 44 C: 48	Rx: 68% C: 75%	Government agency (main funder); pharmaceutical company
Preisinger, 1995,[203] 2001[201]	2	3	3	2	1	3	14/18 (78)	Rx: 82 C: 64	Rx: 48% C: 71%	Austrian National Bank
Sinaki, 2002[202]	1	3	2	2	0	3	11/15 (73)	Rx: 34 C: 31	Rx: 100% C: 100%	National agency; research foundation; charitable trust

TABLE 195 *Exercise: adverse effects*

Study	Exercise-related injuries	Other adverse events	Withdrawals/discontinuation due to adverse events
Bravo, 1996[198]	None reported	None reported	None reported
Ebrahim, 1997[197]	The brisk walking group experienced more falls than the control group (an excess of 15.2 falls per 100 person-years over the course of the study)	Not reported	One withdrawal was due to exercise-related trauma; this was not attributed to a study group. Overall, a further ten withdrawals were due to illness and two to death
McMurdo, 1997[200]	13 women in the treatment group had falls (15 falls in all), compared with 21 in the calcium group (31 falls) ($p = 0.158$)	Not reported	None reported
Preisinger, 1995,[203] 2001[201]	None reported	None reported	Three women had to be excluded from the follow-up because of adverse events (two because of Parkinson's disease and one because of bone metastasis caused by breast cancer)
Sinaki, 2002[202]	None reported	None reported	One woman had died by the time of the follow-up
Winegard, 2001[199]	None reported	None reported	None reported

Appendix 11

Assessing the quality of modelling within the submissions

The *BMJ* checklist for economic evaluations[206] was used to assess the quality of the submitted models, the questions of which are duplicated below. The reviewer's comments are produced separately for each model along with discussion on the likely impact of different methodologies or assumptions. Where the questions have been answered appropriately and sufficiently the term 'OK' has been used.

Quality assessment questions

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

Alendronate

1. OK.
2. OK.
3. OK.
4. From the perspective of Merck Sharpe and Dohme, the focus is upon proving the cost-effectiveness of alendronate against a no treatment option (consisting of calcium and vitamin D supplements). No attempts have been made to see whether any alternative treatments may be more cost-effective than their product.
5. OK.
6. OK.
7. The authors have acknowledged the importance of incorporating first order

uncertainty within the model. However, it is unclear whether the main reason for conducting an individual patient model (the increased risk of subsequent fractures following an initial fracture) is included in their first order model. The similarity between the results from an individual patient model and a cohort model is reported; however, no data are given to provide evidence for this. If the increased risk of subsequent fractures has been omitted, the 'true' difference between these approaches is likely to be underestimated, as there will be no difference in fracture risk between the two methodologies. In such circumstances the results from a cohort approximation could be unsound. It is appreciated, however, that a full individual patient model would have been very difficult within the review period.

8. OK.
9. OK.
10. Not applicable.
11. OK.
12. OK. However, for reasons discussed within the utility section of the report, the values used in the appraisal team model differ (considerably for vertebral fracture). Within their sensitivity analyses the authors use values similar to that in the appraisal team model. The base-case scenario adopted is far more favourable to the drug than that used in the appraisal team.
13. OK, although the reservations the review team had regarding the small sample size used to derive utility values for vertebral fractures have not been discussed.
14. Not applicable.
15. Not applicable.
16. This has not been done. However, this value has not been recorded in the appraisal team model.
17. OK. Analyses have been undertaken assuming relative risks compared with the general population, rather than assessing individuals at specific *T*-score levels.
18. Yes. The model uses values inflated to 2000/01. The appraisal team uses values inflated to 2001/02, which will be more beneficial to the intervention, owing to the higher cost of fractures. The cost data used in the models differ significantly for hip fracture, with the submission value being far greater than that of the appraisal teams. This is due to the submission model assuming that 10% of people suffering a hip fracture will remain in a nursing home for the remainder of their life, regardless of age. Data from the UK used in the appraisal model[19] show this figure to be strongly related to age, being 0% below the age of 60, 4% below the age of 80 and 12% afterwards. At lower ages it is clear that the submission model favours the intervention, particularly given the high cost associated with nursing homes. Costs for clinical vertebral fracture and wrist fracture are broadly comparable. The submission model also attaches a cost to morphometric fractures, which is approximately 70% that of a clinical fracture.
19. OK.
20. OK.
21. As detailed in 17, 12 and 18, the key parameters of fracture incidence are incorrect, utility decrement suffered following a vertebral fracture, and the costs of a hip fracture are greater than the appraisal team's value, respectively. Other key differences between the baseline models were:

    - The submission model includes morphometric vertebral fractures; however, the appraisal model does not. The submitted model favours the intervention.
    - The appraisal model includes proximal humerus fractures; however, the submission model does not. The appraisal model favours the intervention.
    - The submission model includes only patients with a vertebral fracture in the severe osteoporosis group; however, the appraisal model includes patients with vertebral, hip, wrist and proximal humerus.
    - Both models assume a 5-year treatment period. The appraisal model assumes a full treatment for this 5-year period; it is unclear from the submission whether an assumption of full effect is made or a linear increase (Figure 36 of the submission) is made. After treatment has been stopped the appraisal model assumes a 5-year linear decrease to the risk of no treatment; the submission model assumes an additional 2 years of full effect, before a 3-year linear decrease to the risk of no treatment. Owing to the ambiguity over the initial 5-year period it is not clear which model favours the intervention.
    - The submission model assumes that the subsequent annual costs associated with vertebral fractures have a duration of 3 years. The appraisal model assumes that these costs are continued for the duration of the model.
    - The percentage of hip fractures that result in death is different between the

submission model and the appraisal model. The submission model uses relative risks from Swedish data,[9] whereas the appraisal model uses data from the Second East Anglian Audit of hip fracture[19] adjusted by data from Parker and Anand.[20] It is not clear which approach is more favourable to the intervention.
- It is unclear whether death from vertebral fracture is included in the submission model. Text in Section 3.3 alludes to not, however the method of calculation is given in Section 3.8 of the submission.[42]
- The calculation of utility decrement when a patient suffers multiple events has been estimated differently. The submission model just uses the greatest decrement, whereas the appraisal model uses the utility multipliers for each event. In this instance the appraisal model is more favourable to the intervention.

22. The submission model assumes the time horizon to be the patient lifetime or 100 years of age. The appraisal model assumes a time horizon of 10 years. The assumption made by the submission model favours the intervention.
23. OK.
24. OK.
25. Not applicable.
26. Not explicitly, although a cost-effectiveness acceptability curve is presented to aid decision-makers.
27. OK.
28. OK. All the main parameters are included.
29. OK, although owing to the difference in the assumption regarding the effect of vertebral fractures the sensitivity applied in the submission model rarely ventures into the values assumed by the appraisal team.
30. As detailed in 4, no other osteoporosis treatments have been evaluated in cost-effectiveness terms.
31. OK, with the caveat that only one treatment was evaluated.
32. OK.
33. OK.
34. OK.
35. OK.

Etidronate

1. OK.
2. OK.
3. OK.
4. Economic analyses have been conducted only on the bisphosphonate class as a whole, or on etidronate separately. No other osteoporosis treatments have been evaluated in cost-effectiveness terms allowing comparisons with etidronate.
5. OK.
6. OK.
7. OK. However, no attempts at first order uncertainty have been conducted. See point 7 in the critique of the alendronate submission and the report text for more discussion on the potential differences between individual patient models and cohort Markov models.
8. The assumption that etidronate has the same efficacy as the other bisphosphonates may not be secure. This assumption dramatically affects the cost per QALY ratio, in many cases changing the drug from cost-effective to non-cost-effective. The use of a weighted cost for the bisphosphonate class is also theoretically questionable, since were the assumption to be made that the drugs have the same efficacy, it would be clear that a cost-minimisation approach (that of taking the cheapest intervention) should be used.
9. OK.
10. No additional details were given.
11. OK.
12. OK. However, it is noted that the disutility associated with a hip fracture in the initial year is far greater in the submission model than in the appraisal model. The submission model is more favourable to the intervention. Utility adjustments due to wrist or clinical vertebral fractures are broadly comparable between the submission and the appraisal models.
13. OK. The papers from which the data have been taken are all referenced.
14. Not applicable.
15. Not applicable.
16. This has not been done. However, this value has not been recorded in the appraisal team model.
17. OK. Analyses have been undertaken assuming relative risks compared with the general population, rather than assessing individuals at specific *T*-score levels.
18. OK. It is noted that the value used for the cost of a hip fracture is far greater in the submission model than that assumed in the appraisal model, owing to the model using the data from Burge and colleagues,[5] which assume that 7% of patients with a hip fracture will enter a nursing home, regardless of age. Data from the UK used in the appraisal

model[19] show this figure to be strongly related to age, being 0% below the age of 60, 4% below the age of 80 and 12% afterwards. At lower ages it is clear that the submission model favours the intervention, particularly given the high cost associated with nursing homes. Costs for clinical vertebral fracture and wrist fracture are broadly comparable.

19. OK.
20. OK.
21. As detailed in 17, 12 and 18, the key parameters of fracture incidence are incorrect, utility decrement suffered following a vertebral fracture, and the costs of a hip fracture are greater than the value in the appraisal model, respectively. Other key differences between the baseline models were:

    - The submission model includes morphometric vertebral fractures; however, the appraisal model does not. The submitted model favours the intervention.
    - The appraisal model includes proximal humerus fractures; however, the submission model does not. The appraisal model favours the intervention.
    - The characteristics of patients entering the model differ between the two models. The submitted model of the bisphosphonate class assumes that patients with at least one of osteoporosis, an unequivocal fracture and osteopenia and a fracture are treated, and that all patients have three times the average risk for their age group. The submission model assumes that patients are at the threshold for osteoporosis and calculates the risk of fracture from age, *Z*-score and fracture status. It is likely that the submission model favours the intervention at higher ages and favours no treatment at lower ages compared with the appraisal model, owing to the decrease in *Z*-score with age relative to the threshold of osteoporosis. The submitted model for etidronate uses a different methodology, similar to that of the appraisal model.
    - The submission model has amalgamated patients who have severe osteoporosis and those who have osteoporosis. It is expected that the former group has higher fracture risks than the latter and it is possible at certain ages that the combined group may be cost-effective; however, those with osteoporosis only may not be. This circumstance has been avoided in the appraisal model by treating these groups independently.
    - Both models assume a 5-year treatment period. The appraisal model assumes a full treatment for this 5-year period; it is unclear from the submission whether any sustained effect following the treatment period has been assumed. After treatment has been stopped the appraisal model assumes a 5-year linear decrease to the risk of no treatment. If no sustained effect has been assumed in the submission model then the appraisal model favours the intervention.
    - The percentage of hip fractures that result in death is different between the submission model and the appraisal model. The submission model uses the rates reported by Keene and colleagues,[3] whereas the appraisal model uses data from the Second East Anglian Audit of hip fracture[19] adjusted by data from Parker and Anand.[20] It is expected that the submission is more favourable to the intervention.
    - Data on the incidence of future fractures following an initial fracture have been taken from van Staa and colleagues[222] in the submission model and from Klotzbuecherand colleagues[15] in the appraisal model. The appraisal model is less favourable to interventions at younger ages and more favourable at older ages compared with the submission model.

22. OK.
23. OK.
24. OK.
25. Not applicable.
26. Only one-way sensitivity analysis has been conducted.
27. OK, although a more thorough approach than one-way sensitivity analyses would be recommended.
28. OK.
29. OK. However, the cost of a hip fracture was never lowered to the value assumed in the appraisal model.
30. As detailed in 4, no other osteoporosis treatments have been evaluated in cost-effectiveness terms.
31. The approach taken was in omitting non-bisphosphonate osteoporosis treatments and with the assumption that etidronate has the same efficacy as other bisphosphonates. In this instance incremental analyses can be performed that would result in the cheaper intervention being recommended. When the

assumption of equal efficacy is relaxed, incremental analysis between etidronate and the remaining bisphosphonates could have been undertaken.
32. OK.
33. OK.
34. OK.
35. OK.

Raloxifene

1. OK.
2. OK.
3. OK.
4. From the perspective of Eli Lilly and Company the focus is on proving the cost-effectiveness of raloxifene against a no treatment option (consisting of calcium and vitamin D supplements). No attempts have been made to see whether any alternative treatments may be more cost-effective than their product.
5. OK.
6. OK.
7. OK. However, no attempts at first order uncertainty have been conducted. See point 7 in the critique of the alendronate submission and the report text for more discussion on the potential differences between individual patient models and cohort Markov models.
8. OK. The submission model has assumed that raloxifene has no effect on non-vertebral fractures owing to the lack of significance. The appraisal model has used the data and confidence intervals that include an increase in hip fractures, and evaluated the no effect option in sensitivity analyses. The submission model favours the intervention.
9. OK.
10. Not applicable.
11. OK.
12. OK. However, it is noted that the disutility associated with clinical vertebral fractures and morphometric fractures in the initial year is far greater in the submission model than in the appraisal model. The submission model uses a disutility for a vertebral fracture that is greater than for a hip fracture. The submission model is more favourable to the intervention. Utility adjustments due to wrist or clinical vertebral fractures are broadly comparable between the submission and the appraisal model. The appraisal model has used utility decrements that are greater for the events of breast cancer and CHD than has the submission model. In this aspect the appraisal model favours the intervention.
13. OK, although the reservations the review team had regarding the small sample size used to derive utility values for vertebral fractures have not been discussed.
14. Not applicable.
15. Not applicable.
16. OK.
17. OK. Analyses have been done, assuming relative risks compared with the general population, rather than assessing individuals at specific *T*-score levels. The submission model has used the average value for breast cancer incidence, which is approximately 5% lower than the adjusted figure used in the appraisal model. The submission model only adjusts for the decreased risk in breast cancer due to low BMD as a sensitivity analysis, which is the base-case analysis in the appraisal model. The submission model favours the intervention.
18. OK. It is noted that the value used for the cost of a hip fracture is far greater in the submission model than that assumed in the appraisal model owing to an assumption made in the submission that 10% of hip fractures result in the patient entering a nursing home. Data from the UK used in the appraisal model[19] show this figure to be strongly related to age, being 4% below the age of 80 and 12% afterwards. At lower ages it is clear that the submission model strongly favours the intervention, particularly given the high cost associated with nursing homes. In addition, the submission model has assumed a cost for morphometric fractures that is approximately equivalent to that of fractures that come to clinical attention. The appraisal model assumes no cost for morphometric fractures. The submission model assumes higher costs for CHD events than the appraisal model. The submission model favours the intervention.
19. OK. The submission model used prices set to the year 2000/01, whereas the appraisal team model used prices set to the year 2001/02. The appraisal model favours the intervention.
20. OK.
21. As previously detailed, the fracture incidence rate has been incorrectly calculated, the reduction in utility following a vertebral fracture (clinical or morphometric) is far greater than in the appraisal model, as is the assumed cost of a hip fracture. Other differences in the baseline models were:

    - The appraisal model includes proximal humerus fractures; however, the submission

model does not. The appraisal model favours the intervention.
- The characteristics of patients entering the model differ between the two models. The submitted model assumes patients with specified relative risks compared with the population. The appraisal model assumes patients at the threshold for osteoporosis and calculates the risk of fracture from age, *Z*-score and fracture status.
- The submission model assumes that 23% of deaths in the year following a hip fracture are causally related to the fracture, assuming data from Sweden[9] on mortality. The appraisal model uses data from the Second East Anglian Audit of hip fracture[19] adjusted by data from Parker and Anand.[20] It is not clear which approach is more favourable to the intervention.
- The submission model immediately aggregates the costs and utility decrement over a 3-year period for each patient suffering a vertebral fracture. This will overestimate costs and utility decrements were a patient to die within this period.
- The submission model assumes that there can be death due to vertebral fracture (a relative risk of 1.95 for a clinical fracture). This is not included in the appraisal model and has been explored in the sensitivity analyses.
- The submission model uses only invasive breast cancer, whereas the appraisal model uses all breast cancer. Given the reduced efficacy of the drug in all breast cancer, but the greater number of all breast cancers, it is unclear which model is more favourable to the intervention.
- The submission model assumes that there is no relationship between low BMD and a reduced incidence of breast cancer based on the apparent general population risk of breast cancer found in an RCT.[143] The appraisal model uses the decrease in breast cancer incidence related to low BMD as previously reported by Cauley and colleagues[32] and given support by Zhang and colleagues,[33] which resulted in a reduction of 47% at the age of 50 years, declining to 10% at the age of 80 for women at the threshold for osteoporosis.
- The risk of mortality following breast cancer in the submission model has been derived from Swedish data.[231] The appraisal model uses data from the UK.[31] It is unclear which model favours the intervention.

22. OK. The time horizon until the patient reaches the age of 100 years or death will be more favourable to the intervention.
23. OK.
24. OK.
25. Not applicable.
26. Only one-way sensitivity analyses were performed.
27. OK.
28. OK, although a more thorough approach than one-way sensitivity analyses would be recommended.
29. OK. although no sensitivity has been undertaken around the additional cost assumed owing to nursing home admission at younger costs, nor are there adequate sensitivity analyses on the importance (or not) of morphometric fractures.
30. OK.
31. OK, with the caveat that only one treatment was evaluated. No incremental analyses compared with bisphosphonates have been conducted.
32. OK.
33. OK.
34. OK.
35. OK.

Risedronate

Two models were submitted for Risedronate (Proctor & Gamble).[43] One is very similar to that for etidronate and thus will not be reassessed. The second model (Kanis and colleagues) will be assessed.

1. OK.
2. OK.
3. OK.
4. Analysis has been confined to risedronate alone. No other osteoporotic treatments have been analysed.
5. OK.
6. OK.
7. OK. The model presented allows the residual costs and effects of hip fracture to be maintained, but cannot, owing to its cohort Markov approach, allow vertebral fractures or wrist fractures to be sustained after a hip fracture. In this respect the modelling structure will underestimate the number of vertebral and wrist fractures suffered. The authors acknowledge that an individual patient approach (as undertaken in the appraisal model) would counter this problem. The rationale of not taking this approach

owing to the complexity, transparency and potential data shortfalls is questionable; however, the time required to calculate results may have been prohibitive.
8. OK.
9. OK.
10. Not applicable.
11. OK.
12. OK. It is noted that the disutility values associated with clinical vertebral fractures are far higher than those used in the appraisal model. The submitted model favours the intervention.
13. OK, although the reservations the review team had regarding the small sample size used to derive utility values for vertebral fractures have not been discussed.
14. Not applicable.
15. Not applicable.
16. Not given. These data were also not recorded in the appraisal model.
17. OK. The submission model has adjusted the fracture rates based on the incidence of fractures in healthy women rather than that of the average population. The estimates between the incidence rates used in the submission model and the appraisal model are broadly comparable.
18. OK. It is noted that the value used for the cost of a hip fracture is far greater in the submission model than that assumed in the appraisal model, owing to an assumption made in the submission that 10% of hip fractures result in the patient entering a nursing home. Data from the UK used in the appraisal model[19] show this figure to be strongly related to age, being 4% below the age of 80 and 12% afterwards. At lower ages it is clear that the submission model strongly favours the intervention, particularly given the high cost associated with nursing homes. In addition, the submission model has assumed a cost for morphometric fractures that is approximately equivalent to that of fractures that come to clinical attention. The appraisal model assumes no cost for morphometric fractures. The submission model is more favourable to the intervention.
19. Costs were inflated to the year 2000/01. Costs in the appraisal model have been inflated to the year 2001/02. The appraisal model is more favourable to the intervention.
20. OK.
21. As previously detailed, the reduction in utility following a vertebral fracture (clinical or morphometric) is far greater than in the appraisal model, as is the assumed cost of a hip fracture. The submission model also allows death due to a vertebral fracture. Other key differences in the baseline models were:

    - The submission model includes morphometric vertebral fractures; however, the appraisal model does not. The submitted model favours the intervention.
    - The appraisal model includes proximal humerus fractures; however, the submission model does not. The appraisal model favours the intervention.
    - The submission model assumes that 23% of deaths in the year following a hip fracture are causally related to the fracture, assuming data from Sweden.[9] The appraisal model uses data from the Second East Anglian Audit of hip fracture[19] adjusted by data from Parker and Anand.[20] It is not clear which approach is more favourable to the intervention.
    - The submission model immediately aggregates the costs and utility decrement over a 3-year period for each patient. This will overestimate costs and utility decrements were a patient to die within this period.
    - The submission model assumes that there can be death due to vertebral fracture (a relative risk of 1.95 for a clinical fracture). This is not included in the appraisal model and has been explored in the sensitivity analyses.
    - The submission model includes only patients with a vertebral fracture in the severe osteoporosis group; however, the appraisal model includes patients with vertebral, hip, wrist and proximal humerus.
    - The submission model assumes that the subsequent annual costs associated with vertebral fractures have a duration of 3 years. The appraisal model assumes that these costs are continued for the duration of the model.

22. OK.
23. OK.
24. OK.
25. Not applicable.
26. None given; however, cost-effectiveness acceptability curves (based on changing the efficacy of the intervention) have been presented.
27. OK.
28. OK.
29. OK. However, some potentially key parameters, such as the cost of a hip fracture, have not been analysed.

30. OK.
31. OK, with the caveat that only one intervention was evaluated.
32. OK.
33. OK.
34. OK.
35. OK.

Teriparatide

The treatment duration of teriparatide is significantly different to the other interventions (18 months compared with 5 years). As such, an assumption was made so that the results for this drug could be calculated from the Gaussian process meta-model. The submission model assumes a 3-year period of full efficacy with a linear decline over 3.5 months to the risks associated with no treatment; the appraisal model assumes a 5-year period of full efficacy and 2 years of linear decline to the level of no treatment. This assumption will be favourable to the intervention.

1. OK.
2. OK.
3. OK.
4. OK. Analysis has been compared to teriparatide alone. No other osteoporosis treatment has been analysed in cost-effectiveness terms.
5. OK.
6. OK.
7. OK. Both the submission model and the appraisal model are based on individual patient methodologies. The submission model iterates on a 6-monthly cycle, the appraisal model on 1-yearly cycles. The submission model allows for multiple fractures to be suffered, whereas the appraisal model allows only one event per cycle. The appraisal model is slightly less favourable to the intervention.
8. OK. However, only point estimates are used, rather than the wide confidence intervals for each relative risk parameter. All non-vertebral fractures have been classed as homogeneous, whereas the appraisal model uses relevant data for hip, wrist and proximal humerus sites.
9. OK.
10. Not applicable.
11. OK.
12. OK. It is noted that the disutility values associated with clinical vertebral fractures are far higher than those used in the appraisal model. The disutility value for wrist fractures is also higher than in the appraisal model. The submitted model favours the intervention.
13. OK, although the reservations the review team had regarding the small sample size used to derive utility values for vertebral fractures have not been discussed.
14. Not applicable.
15. Not applicable.
16. Not given. These data were also not recorded in the appraisal model.
17. OK. Analyses have been done, assuming relative risks compared with the general population, rather than assessing individuals at specific *T*-score levels.
18. OK. It is noted that the value used for the cost of a hip fracture is far greater in the submission model than that assumed in the appraisal model, owing to an assumption made in the submission that 10% of hip fractures result in the patient entering a nursing home. Data from the UK used in the appraisal model[19] show this figure to be strongly related to age, being 4% below the age of 80 and 12% afterwards. At lower ages it is clear that the submission model strongly favours the intervention, particularly given the high cost associated with nursing homes. The submission model is more favourable to the intervention. The submission model assumes that costs due to a vertebral fracture return to zero after 3 years, whereas the appraisal model assumes that these costs will persist throughout the modelling horizon. In this aspect the appraisal model favours the intervention.
19. OK. The submission model used prices set to the year 2000/01 whereas the appraisal team model used prices set to the year 2001/02. The appraisal model favours the intervention.
20. OK.
21. The non-adjustment of the average fracture rate for that of healthy women and the increased cost of hip fracture in the submission model have already been noted. Other key differences between the models were:

    - The appraisal model includes proximal humerus fractures; however, the submission model does not. The appraisal model favours the intervention.
    - The characteristics of patients entering the model differ between the two models. The submitted model assumes patients with vertebral fracture only. The appraisal model assumes that patients with severe osteoporosis have suffered an assortment of

vertebral, hip, wrist and proximal humerus fractures.
- The submission model assumes that there can be death due to vertebral fracture. This is not included in the appraisal model and has been explored in the sensitivity analyses.
- The submission model calculates deaths following a hip fracture from a statistical formula; the appraisal model uses UK data.[19] It is not clear which approach is more favourable to the intervention. The appraisal model assumes that all deaths are related to the fracture. The appraisal model uses data from Parker *et al*.[20] to estimate those deaths that were attributable to the fracture. In this aspect the submission model is more favourable to the intervention.
- The submission model assumes that the elevated risk of fracture following initial fractures dissipates with time and is calculated from a statistical formula. The appraisal model assumes that this elevated risk persists for the modelling horizon. It is unclear which model is more favourable to the intervention.

22. OK. The submission model starts with women aged 69 years and follows them until death or the age of 100 years. The appraisal model uses a time horizon of 10 years. The submission model favours the intervention.
23. OK.
24. OK.
25. Not applicable.
26. None given.
27. OK. However, only one-way sensitivity analyses were performed. A more thorough multiway sensitivity approach is recommended.
28. OK. However, a key variable, the age of the patient, has not been varied. The appraisal model has undertaken analyses at the ages of 50, 60, 70 and 80 years.
29. OK.
30. OK.
31. OK, with the caveat that only one intervention was evaluated.
32. OK.
33. OK.
34. OK.
35. OK.

Appendix 12

Modelling methodology

The first example concerns the accuracy with which the probability of fractures can be calculated, based on the patient history. There is a breadth of published literature that indicates that an initial fracture greatly increases the risk of subsequent fractures.[15] Implementing these relationships within an individual patient model is far simpler than in a cohort model. Consider an example of two identical osteoporotic patients at the cohort model initiation, who are simulated for 5 years of life. Patient A may suffer no fractures for the first 4 years and suffer a wrist fracture in the fifth year. Patient B suffers no fractures in the first 2 years and then suffers a hip, vertebral and wrist fracture in the next 3 years. In a simple cohort model both patients now reside in the wrist fracture state. However, if the values from the available data are used, patient B would have a much greater risk of vertebral fracture and an increased risk of hip fracture than patient A. Without adjusting for this increased probability of fracture, the model would underestimate the number of fractures that occur.

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

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

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

The only alternative manner in which all data can be taken into consideration is by the use of a decision tree. If a simple model with only four transition states is assumed (no fracture event, hip fracture, vertebral fracture and wrist fracture), the tree would have 4^{10} branches in a 10-year period in order that all conceivable combinations of events are recorded. This totals over 1 million branches at year 10. Clearly, this number would be greatly increased with the addition of extra states (breast cancer, other fracture states) and would need to be duplicated with the tracking of residential status (community or nursing home). To replicate the patient-based model presented in this report using a decision-tree format would require over 1000 million branches to maintain accuracy. This would essentially be what was required to maintain the structure in a cohort approach.

Removing noise from the individual patient results and producing a meta-model through a Gaussian process

In order that a distinction could be made between variations in the results due to random events

TABLE 196 *Additional impact of incorporating the fall time of the interventions*

Age (years)	Additional impact of assuming a 5-year fall time compared with the 5-year treatment period (costs)	Additional impact of assuming a 5-year fall time compared with the 5-year treatment period (QALYs)	Additional impact of assuming a 1-year fall time compared with the 5-year treatment period (costs)	Additional impact of assuming a 1-year fall time compared with the 5-year treatment period (QALYs)
50	36%	49%	8%	10%
60	35%	47%	8%	10%
70	33%	44%	8%	9%
80	24%	33%	7%	8%

(such as premature death) and those variations caused by the uncertainties in the true relative risks for the efficacy of each drug, as indicated by the 95% confidence intervals, a large number of patients had to be simulated and the results would be relatively robust. For the patients suffering severe osteoporosis 8000 patients were simulated; for the solely osteoporotic population 15,000 patients were simulated owing to the lower absolute risk of events. These numbers of patients significantly reduced the noise in the results, but at the expense of increased computational time (approximately 1 hour and 2 hours, respectively).

Given the extensive sensitivity analyses that needed to be conducted owing to the uncertainty in the efficacies of the interventions, continually using the individual patient model to calculate the costs and QALYs associated with a particular set of relative risks was not practical, if it was assumed that 1000 sampled combinations of the relative risks for each intervention would be required to provide an adequate range of cost-effectiveness values.

The methodology used to counter this problem was Gaussian process modelling,[210] which is a non-parametric technique that forms a statistical relationship between the input data and the output data.

To inform the Gaussian model the individual patient model was run approximately 160 times at each age for both severe osteoporotic and osteoporotic patients using different values for the parameters that were to be varied in the sensitivity analyses. These parameters were the relative risks of each clinical condition (the fractures, CHD and breast cancer), the costs and QALY multipliers associated with each condition and the fall time associated with treatment. The Gaussian model was formulated to calculate explicitly the interactions between the relative risks and their respective costs and QALY multipliers. Without using such interactions the impact of changing the cost or QALY multiplier for a condition would be constant regardless of the efficacy of the intervention on that condition.

From these data the Gaussian model could be formulated and the statistical relationship defined, allowing instant estimates of the cost and QALYs associated with any parameter set.

The fall time was difficult to model within a Gaussian process since it would need to incorporate an interaction term with each of the relative risks. This is required as the effects of a fall time would be to accentuate either the benefit gained where a relative risk was less than 1, or the detriment associated with relative risks greater than 1.

To limit the number of variables entered into the Gaussian model, a decision was made to model the fall time outside the Gaussian model. The methodology for this was based on the assumption that the additional gain or loss would be proportional to the gain or loss within the initial 5-year treatment period. To calculate the additional gain or loss, the number of patients alive at each year was calculated and discounted at a rate of 1.5% for QALYs and 6% for costs. The number of patient-years was summated for the 5-year treatment period. This figure was also calculated for the 5 years associated with the fall time and halved to approximate the linear decline in efficacy.

By dividing the number of patient-years over the first 5-year period by that related to the fall-time period, an estimation of the additional impact that the fall time would have can be calculated. These data are shown in *Table 196* for a 5-year fall time, and also for a 1-year fall time assumed to be applicable for teriparatide. These additional impacts were added to every parameter set analysed.

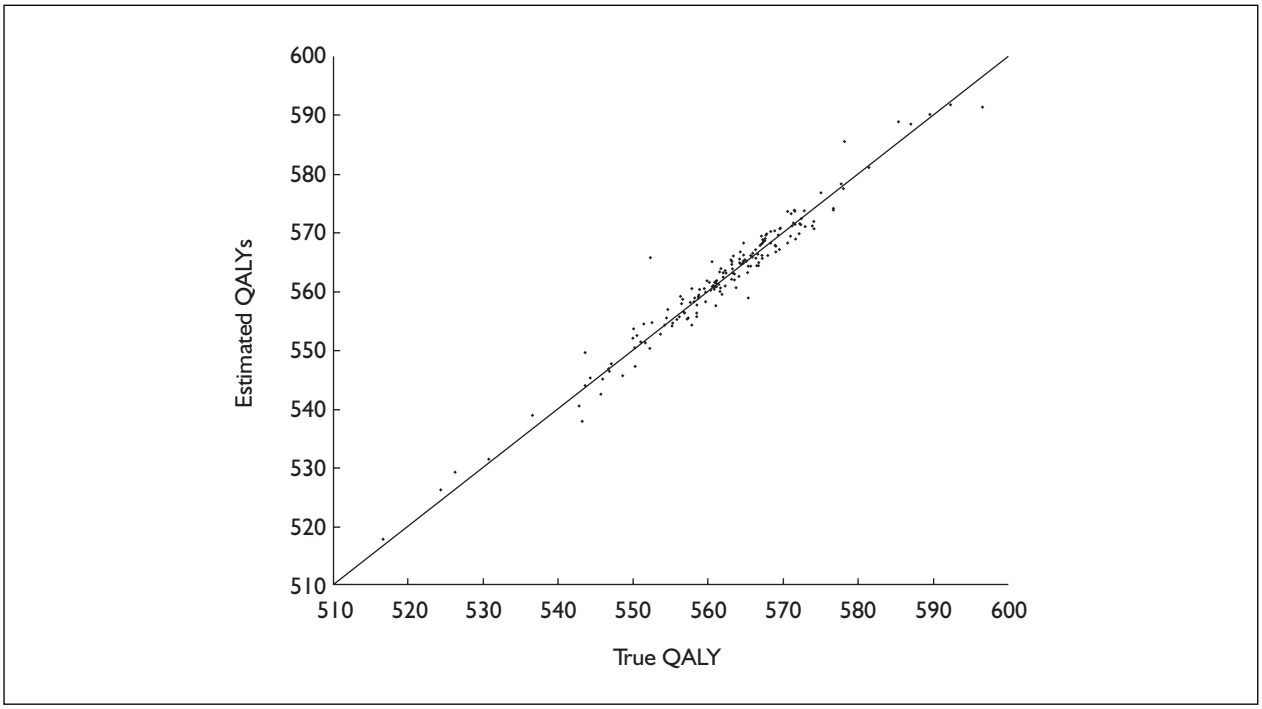

FIGURE 63 *Cross-validation of the Gaussian model using data at 70 years of age, assuming no prior fracture*

The accuracy of the results approximated by the Gaussian process model was good. Cross-validation exercises were performed by removing each data point in turn and fitting a model to the reduced data set. The estimate of the Gaussian estimated output at the omitted input configuration was then compared with the true output. The absolute percentage errors were typically very small. The statistic of the difference in the predicted result and the true result, divided by the range of the true results, was used to assess accuracy. This was less than 2% for both costs and QALYs. These mean figures include larger errors for data points with extreme input configurations, such as all relative risks being set to 6, or very high individual values for relative risks such as wrist set to 4, or extreme values used for the utility multipliers of events. These points are more isolated (i.e. when they are removed from the data set there are no points at similar levels to correct a linear fit), and the errors will be less for points within the normal range of efficacies for the intervention. The distributions of errors were approximately symmetrical around zero, and thus the mean values of costs and QALYs for an intervention are unlikely to be affected by the slight inaccuracy associated with the Gaussian process approximation.

The results for the cross-validation exercise for QALYs at 70 years of age, assuming no prior fracture, are shown in *Figure 63*.

Appendix 13

Calculation of the additional QALYs lost through a death from a hip fracture or through breast cancer

The model builds on the work undertaken for an HTA report[207] that used a time horizon of 10 years. This, however, would mean that any mortality prevented within this period would not be given full weight, which would bias against beneficial treatments, and adjustments were needed to correct for this error.

To adjust for this factor, an estimation of the QALYs that could be gained by prevention of mortality, at each age, was made. Calculations were only needed from the end of the 10-year modelling horizon, since any QALY impacts within this period would be explicitly calculated within the model. The methodology for this was as follows.

The life expectancy for a patient at the threshold of osteoporosis was calculated from standard life tables, as shown in *Table 11* of the main report. It was assumed that any increase in mortality rate due to low bone mass would continue until death or the age of 110 years.

Since the final QALY score of each patient within the individual patient model was not estimated by the Gaussian model, it was assumed, slightly favouring the interventions, that individuals would have a quality of life score equal to that of the general population, as reported by Kind and colleagues.[215]

Life-years were discounted at 1.5% per annum, starting from the time of intervention.

Using these assumptions, it was estimated that an average patient alive at the end of the model would accrue expected QALYs, as given in *Table 197*.

TABLE 197 *Expected lifetime QALYs for women alive at the end of the model*

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

Having established the gains associated with preventing mortality, the expected number of potentially preventable deaths through hip fracture or breast cancer needed to be calculated.

Calculating the number of preventable hip fracture deaths

The methodology for this was based on the standard rate of hip fracture at each age and the expected mortality associated at that age.

For example, the expected hip fracture rate at 60 years of age, for healthy women at the threshold of osteoporosis, is estimated to be 0.1%. When analysing patients with severe osteoporosis it was assumed that this risk could be doubled, in accordance with data reported by Klotzbuecher and colleagues.[15]

This would equate to an estimate of the hip fracture rate of 0.2% per annum, or 1.0% over a 5-year treatment period, assuming no additional mortality, which is one hip fracture for a cohort of 100 women.

The mortality rate following hip fracture is estimated to be 6% at age 60 (*Table 7* of the main report), which can result in a maximum of 0.06 hip fractures that were preventable over the intervention period. The number that were preventable is assumed to be equal to the sampled relative risk for each treatment; thus, if a relative risk of hip fracture of 0.5 was estimated, then it was assumed that 0.03 deaths associated with hip fractures would be saved. Where the relative risk was above 1, the model assumed that an additional number of deaths would occur and subtracted the expected QALYs from that estimated for the intervention.

The expected numbers of additional QALYs for patients with severe osteoporosis suffering death from hip fracture are given in *Table 198*.

TABLE 198 *Maximum number of QALYs assumed preventable due to hip fracture mortality*

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

A similar methodology was used to calculate the maximum number of QALYs that could be saved by preventing breast cancer mortality. These data are given in *Table 199*. These figures are greater than those for hip fracture at younger ages since, although the incidence rates of breast cancer and hip fracture are comparable at an early age, the assumed mortality associated with breast cancer (32%) is much greater. At older ages both the incidence and mortality associated with hip fracture greatly increase.

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

It was assumed that all deaths from vertebral fracture would happen in year 3, the midpoint of the treatment period, assuming a 66% increase in the mortality rate in the year of a vertebral fracture, as reported by Center and colleagues[21] and assuming that all of these deaths were attributable to the vertebral fracture. By

TABLE 199 *Maximum number of QALYs assumed preventable due to breast cancer mortality*

Age (years)	Maximum QALYs gained from preventing breast cancer mortality
50	2.784
60	2.336
70	1.135
80	0.323

TABLE 200 *Maximum number of QALYs assumed preventable due to vertebral fracture mortality*

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

calculating the expected number of vertebral fractures per year and the expected associated mortality assuming 5 years of no treatment, the maximum number of QALYs that could be prevented was estimated. These data are shown in *Table 200*.

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

Appendix 14

Methodological issues in selecting health state values

Review

Table 201 presents the HSUVs found using the search strategy described in the main text. For each HSUV the following is described: health state descriptions, mean and standard deviation of the values, the valuation technique used and the source of the valuations for each of the osteoporosis-related conditions. For comparison, normative HSUV data are presented by age group for the UK.[215] These values were obtained by administering the EQ-5D to over 3000 representative members of the UK general population.[215] The values used by the NOF are presented for comparative purposes, since these are the values commonly used in current economic evaluations.

As a result, there were 102 HSUVs in all, with two valuations for established osteoporosis, 27 for hip fracture, one for hip fracture resulting in home confinement, 30 for vertebral fracture, eight for shoulder fracture, 15 for wrist fracture, two for both vertebral and hip fracture, six for breast cancer and 11 for CHD.

The 85 empirically derived HSUVs for the four fracture conditions (i.e. hip, vertebral, wrist fracture and established osteoporosis) differ considerably from the NOF values obtained by a panel of experts (*Table 201*). The value used in the NOF report[212] for vertebral fractures of 0.97, for example, compares with values ranging from 0.31 to 0.91. These empirical estimates were obtained using a recognised preference elicitation procedure, but there is a considerable range of values for each of the health states. This range reflects a number of differences in the derivation of the estimates, including the source of values, what is being valued, how long after the fracture the assessment was undertaken, the valuation technique and the anchor states used in the valuation task. The selection of estimates for the model involves both technical and values judgements, which are discussed below.

Methodological issues in selecting health state values

The source of values

The studies differ in terms of the samples being asked to undertake the valuations. Some estimates were obtained by asking patients to value their own health state, whereas others were obtained by asking samples of patients to value hypothetical descriptions of the states. Other studies elicited values from samples of professionals[219] or representative samples of the general population.[233] Asking patients to value their own health has the advantage of avoiding the need to describe health states and may ensure they have a better understanding of the impact of the state on their lives. However, the disadvantage is that it limits the source of values to current patients. It has been argued that for the purposes of informing resource allocation, the values of society at large are needed, and hence those studies using a representative sample of the general population would be more appropriate.[234]

What is being valued

Studies asked respondents to value specially constructed vignettes to describe each health state[235] or used generic preference-based measures such as the EQ-5D.[236] The generic preference-based measures come with a set of values already obtained from a general population sample. The state-specific approach has the advantage of potentially being more relevant and sensitive to the condition than the generic measures.[237] The disadvantage is that the descriptions may only represent a proportion of the health states found in a sample of patients and it is not clear how representative they would be of patients with the condition.

Generic preference-based measures have the advantage of being administered on a sample of patients and hence representing the variation in health states found in the population.

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
Healthy osteoporotic	NOF	1.0		Judgement	Panel of experts
	Kind, 1998[215] MVH survey	Age (years) 45–49 0.840 50–54 0.850 55–59 0.802 60–64 0.829 65–69 0.806 70–74 0.747 75–79 0.731 80–85 0.699 >85 0.676	EQ-5D for the general population and hence includes all sources of morbidity found in this population	TTO valuations of EQ-5D hypothetical states with full health and dead as the reference states	General population (n = 3381)
Established osteoporosis (i.e. history of a broken wrist, spinal or hip fracture)	Gabriel, 1999[233]	0.84 (0.29)	Patients who have experienced a non-traumatic vertebral fracture in past 5 years, but not multiple fractures	TTO valuation of own health anchored by best imaginable for age and dead	Patients (n = 75, mean age 76 years)
		0.43 (0.40)	Valuation of hypothetical state constructed from clinician views and focus groups; these include reference to future risk	TTO valuation of hypothetical health state anchored by current health and death transformed using the valuation of own health against perfect health and dead	Non-fracture cases attending a clinic in past 2 years (n = 199, mean age 68 years)
Hip fracture	NOF review, 1998[212]	For first year: 0.3817	Assumes reduction in quality of life from acute care, rehabilitation, home care, GP visits and ambulance	Judgement	Expert panel
		Subsequent years: 0.855	Assumes distribution across disability states		
	Gabriel, 1999[233]	0.68 (0.18)	37 patients who have had a hip fracture in the past 5 years completed the HUI-II	HUI-II valued by SG (estimated from a transformation of VAS)	HUI-II, parents of schoolchildren from Hamilton, Canada (n = 203, mean age 76 years)
		0.61 (0.08)	The above patients completed the QWB	QWB valued by VAS	Representative sample of the general population of San Diego
		0.72 (0.16)	The above patients valued their own health states	VAS	Patients (n = 37)
		0.70 (0.41)	The above patients valued their own health state	TTO anchored by perfect health and death, where perfect health is best imaginable for their age	Patients (n = 37)

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
		0.65 (0.45)	Patients' own valuation of their hip fracture state which they regarded as worse than a hypothetical 'disabling' fracture state	TTO anchored by perfect health and death, where perfect health is best imaginable for their age	Patients (n = 33, mean age 76 years)
		0.28 (0.37)	Hypothetical 'disabling' hip fracture state	TTO anchored by own health state and death and the latter transformed using their valuation of their own health state (itself anchored against best imaginable for health and death)	Recent clinic attendees who have never had a fracture (n = 198, mean age 68 years)
	Salkeld, 2000[235]	0.31 (IQR 0.0–0.65)	Based on a description of life after a 'good' hip fracture	TTO anchored by a hypothetical health state for someone of similar age to the respondent and death	Older people at risk of fracture (n = 194, mean age 81 years)
	Murray, 2002[216]	Baseline (n = 117): 0.54 Postfracture: 6 months (n = 103) 0.45 12 months (n = 86): 0.45 24 months (n = 55): 0.5	Patients completed EQ-5D before fracture and then at 6 and 12 months after fracture	TTO valuations of EQ-5D hypothetical states with full health and dead as the reference states	General population (n = 5228, mean age 76 years)
	Tosteson, 2001[244]	Postfracture: 12–24 months (n = 35) 0.48 (95% CI 0.32 to 0.64) > 24 months (n = 32): 0.79 (95% CI 0.66 to 0.92) Overall (average between the two values above) (n=67): 0.63 (95% CI 0.52 to 0.74)	Own health: women with a documented first hip fracture within 5 years who were at least 1 year postfracture	TTO anchored by best imaginable for health and death	Patients (n = 67, mean age 67 years)

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
	Johnell, 2002[243]	Postfracture: 2 weeks (n = 86) 0.42 (0.32) 6 months (n = 65) 0.64 (0.27) 9 months (n = 58) 0.60 (0.31) 2 months (n = 46) 0.58 (0.31)	Patients completed EQ-5D after the fracture	TTO values for EQ-5D generated by social tariff values[236]	Patients (mean age 75 years)
		2 weeks (n = 82) 0.54 (0.20) 6 months (n = 66) 0.64 (0.21) 9 months (n = 55) 0.61 (0.23) 12 months (n = 44) 0.64 (0.23)		VAS	
	Cranney, 2001[242]		Women with a recent hip fracture interviewed at baseline and 2 months' follow-up		Patients (n = 10, median age 79.5 years)
		Baseline: 0.67 (0.12) (95% CI 0.53 to 0.89)	HUI-II	SG (estimated from a transformation of VAS)	
		Postfracture: 2 months: 0.71 (0.09) (95% CI 0.58 to 0.82)			
		Baseline: 0.91 (0.12) (95% CI 0.75 to 1)	Own health	SG	
		2 months: 0.84 (0.18) (95% CI 0.5 to 1.0)			
		Baseline: 0.71 (0.11) (95% CI 0.5 to 0.85)	Own health	VAS	
		2 months: 0.76 (0.18) (95% CI 0.4 to 0.95)			

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
Confined to a nursing home owing to a hip fracture	NOF review, 1998[212]	0.4	Nursing home	Judgement	Expert panel
	Salkeld, 2000[235]	0.05 (no range given)	Based on a description of life after a 'bad' hip fracture that includes being in a nursing home	TTO anchored by a hypothetical health state someone of similar age to the respondent and death	Older people at risk of fracture (n = 194)
Vertebral fracture	NOF review, 1998[212]	0.97	Assumes 33% experience no change, 57% quality of life reduced by 0.5 for 1 month, 10% complete loss and then 0.5 loss for 7 weeks	Judgement	Expert panel
	Gabriel, 1999[233]	0.80 (0.16)	94 patients who have had a vertebral fracture in the past 5 years completed the HUI-II	HUI-II valued by SG (estimated from a transformation of VAS)	HUI-II, parents of school children from Hamilton, Canada (n = 203)
		0.66 (0.09)	Above completed the QWB	QWB valued by VAS	Representative sample of the general population of San Diego
		0.76 (0.17)	Above patients valued their own state	VAS	Patients (n = 94)
		0.81 (0.32)	Above patients valued their own state	TTO anchored by perfect health and death, where perfect health is best imaginable for their age	Patients (n = 94)
		0.68 (0.4)	Patients' own valuation of their fracture state, which they regarded as worse than a multiple vertebral fracture state	TTO anchored by perfect health and death, where perfect health is best imaginable for their age	Patients (n = 24)
		0.31 (0.38)	Hypothetical multiple vertebral fracture state	TTO anchored by own health state and death and the latter transformed using their valuation of their own health state (itself anchored against best imaginable for health and death)	Recent clinic attendees who have never had a fracture (n = 199)

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
	Oleksik, 2000[217]	0.82 (0.21) 0.75 (0.23) 0.74 (0.25) 0.81 (0.18) 0.66 (0.30) 0.78 (0.20) 0.68 (0.34)	Patients with radiographically confirmed fracture in the past 5 years completed the EQ-5D No. 0: $n = 293$ 1: $n = 130$ 2: $n = 69$ 3: $n = 36$ ≥ 4: $n = 60$ Lumbar: $n = 42$ Thoracic: $n = 145$	TTO	General population ($n = 3381$)
	Tosteson, 2001[244]	Postfracture: <12 months ($n = 23$): 0.74 (95% CI 0.57 to 0.92) 12–24 months ($n = 31$): 0.80 (95% CI 0.68 to 0.91) >24 months ($n = 60$): 0.85 (95% CI 0.78 to 0.93) Overall (average value) ($n = 114$): 0.82 (95% CI 0.76 to 0.87)	Women with a documented first vertebral fracture within the past 5 years but no additional non-vertebral fractures in the past 3 years and no hip fracture ever	TTO anchored by best imaginable for health and death	Patients ($n = 114$, mean age 73 years)
	Johnell, 2002[243]	Postfracture: 2 weeks ($n = 40$): 0.21 (0.30) 6 months ($n = 28$): 0.49 (0.28) 9 months ($n = 20$): 0.51 (0.35) 12 months ($n = 12$): 0.57 (0.35)	Patients completed EQ-5D after the fracture	TTO values for EQ-5D generated by social tariff values[236]	Patients (mean age 75 years)

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
		2 weeks (n = 37): 0.44 (0.20) 6 months (n = 28): 0.55 (0.21) 9 months (n = 21): 0.59 (0.23) 12 months (n = 12): 0.59 (0.27)		VAS	
	Cranney, 2001[242]	Baseline: 0.79 (0.22) (95% CI 0.25 to 0.92)	Women with a recent vertebral fracture completing HUI-II	SG (estimated from a transformation of VAS)	
		Postfracture: 2 months: 0.76 (0.14) (95% CI 0.43 to 0.92)			
		Baseline: 0.84 (0.20) (95% CI 0.50 to 1.0) 2 months: 0.91 (0.1) (95% CI 0.7 to 1.0)		SG	
		Baseline: 0.76 (0.13) (95% CI 0.5 to 0.95) 2 months: 0.83 (0.08) (95% CI 0.73 to 0.97)		VAS	
Shoulder fracture	Johnell, 2002[243]	Postfracture: 2 weeks (n = 46): 0.36 (0.30) 6 months (n = 40): 0.69 (0.25) 9 months (n = 37): 0.66 (0.26) 12 months (n = 30): 0.65 (0.29)	Patients completed EQ-5D after the fracture	TTO values for EQ-5D generated by social tariff values[236]	Mean age 72 years

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
		2 weeks (n = 49): 0.50 (0.23) 6 months (n = 39): 0.71 (0.18) 9 months (n = 37): 0.67 (0.21) 12 months (n = 31): 0.70 (0.22)		VAS	
Wrist fracture	NOF review, 1998[212]	1st year 0.96	Assumes 0.7 for 7 weeks	Judgement	Expert panel
		Subsequent years 0.98	Assumes long-term dependency for 2% of cases with reduction in quality of life to 0.7		
	Dolan, 1999[218]	0.982	EQ-5D completed by 50 wrist fracture attendees at an outpatient clinic at first and final visit (average 48-day interval). Implied QALY loss over 1 year assuming a linear progression between initial and last assessment 0.018 (0.014)	TTO valuations of EQ-5D hypothetical states with full health and dead as the reference states	General population (n = 3381, mean age 72 years, range 52–91 years)
	Johnell, 2002[243]	Postfracture: 2 weeks (n = 126): 0.54 (0.27) 6 months (n = 103): 0.76 (0.22) 9 months (n = 92): 0.81 (0.21) 12 months (n = 80): 0.82 (0.20)	Patients completed EQ-5D after the fracture	TTO values for EQ-5D generated by social tariff values[236]	

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
		2 weeks (n = 132): 0.64 (0.22) 6 months (n = 114): 0.73 (0.20) 9 months (n = 95): 0.76 (0.18) 12 months (n = 83): 0.76 (0.20)		VAS	
	Cranney, 2001[242]		Women with a recent wrist fracture completing:		
		Baseline: 0.86 (0.06) (95% CI 0.75 to 0.92)	HUI-II	SG (estimated from a transformation of VAS)	
		Postfracture: 2 months 0.87 (0.07) (95% CI 0.7 to 0.95)			
		Baseline: 0.87 (0.19) (95% CI 0.5 to 1) 2 months: 0.91 (0.15) (95% CI 0.5 to 1.0)	Own health	SG	
		Baseline: 0.84 (0.11) (95% CI 0.63 to 0.95) 2 months: 0.88 (0.07) (95% CI 0.75 to 0.95)	Own health	VAS	
Vertebral fracture and hip fracture	Tosteson, 2001[244]		Women with a documented first hip fracture within 5 years who were at least 1 year postfracture and who had also experienced vertebral fracture afterwards	TTO anchored by best imaginable for age and death	Patients (n = 34, mean age 83 years)

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
		Postfracture: 12–24 months (n = 19): 0.32 (95% CI 0.10 to 0.53) >24 months (n = 15): 0.66 (95% CI 0.44 to 0.88) Overall (average values) (n = 34): 0.47 (95% CI 0.31 to 0.63)			
Breast cancer	Hutton, 1996[219]	0.62 0.33 0.84	Stable disease Progressive disease Partial response to therapy Hypothetical health state descriptions constructed from multidisciplinary group. No variance data given	SG using McMaster ping-pong method	UK oncology nurses (n = 30). Similar figures obtained from nurses in three other countries
	Grann, 1998[245]	0.89 (IQR 0.86–1.00)	No detail offered on the descriptions used	TTO; no protocol detail provided	Convenience sample (n = 54)
	de Haes, 1991[246]	0.65	Health state described as 3 months to 1 year after mastectomy	Crude VAS values, subject to TTO power function	Healthcare workers and cancer experts (n = 27)
		0.17	Terminal illness		
CHD	Oldridge, 1991[247]	0.717–0.767	MI patients at baseline	TTO valuing current state versus full health	Patients
		0.872–0.864	MI patients at 12-month follow-up		
	Tsevat, 1995[248]	0.88	Treatment group	TTO; 10 years in current state versus shorter life in excellent health	Survivors of MI (n = 82)
		0.89	Placebo group Valuing own health state		

continued

TABLE 201 *Empirical estimates of HSUVs for osteoporosis-related health states (cont'd)*

Disease state	Source	HSUV[a]	Methods		
			Health state description	**Valuation technique**	**Source of values**
	Nease, 1995[249]		Angina class:	TTO (VAS and SG also available)	Patients
		1.0	I		
		0.997	II		
		0.929	III/IV		
			Valuing own health		
	Kuntz, 1996[250]	0.89	Mild angina/no CHF	TTO; telephone survey but no further details on procedure	Patients (1051 overall states)
		0.85	Mild angina, CHF		
		0.82	Severe angina		
		0.78	Severe angina, CHF		
			Valuing own health		

[a] HSUV data are presented as mean (SD).
CHF, coronary heart failure; IQR, interquartile range; SG, standard gamble.

Age composition of the studies

The HSUVs do not cover the full range of age groups used in the model. Some studies are limited to one age group[216] and others are based on such small numbers that it has not been possible to estimate reliable age-specific values.

Valuation technique

Another important difference between estimates has been the valuation technique used to elicit health state values, whether directly as part of the study or implicitly through the use of a generic preference-based measure. It is currently recommended that HSUVs should be obtained using a choice-based technique such as standard gamble or TTO, rather than a rating scale.[238]

Anchor states

Studies have also used different anchor states in their valuation tasks. For standard gamble or TTO a health state is valued against two reference states, one better and the other worse. Although most studies have used dead as the worst state, they have described different upper states, such as 'excellent' health, 'full' health (as defined by the EQ-5D or HUI-II), 'best imaginable for your age' or ' your current' health. By convention, death is given a value of zero and the upper anchor state is given a value of one. Where a study has valued a health state using, for example, the best imaginable for age as the upper anchor, the values are higher than those that would be generated from using full health as the upper anchor. Some studies have attempted to correct for this by transforming the results using valuations of the upper anchor, as done by Gabriel and colleagues.[233]

Review of values

General population values

Remarkably few studies give detailed normative data by age. In the USA, there is a set of normative data based on a random survey of the population of one city using the quality of well-being (QWB) scale and the time trade-off (TTO) valuation technique,[239] and in Canada, a version of the HUI has been used in a state-wide health survey.[240] The largest normative data set of health state values in the UK is based on administration of the EQ-5D to over 3000 representative members of the UK general population, and this has been used in the model.[215]

Established osteoporosis

Gabriel and colleagues[233] compare health state TTO valuations by patients who have experienced an atraumatic fracture in the past 5 years (that is not multiple) and the valuation of a hypothetical case by a sample of non-fracture cases. The HSUVs were 0.84 and 0.43, respectively. This large difference can be partly accounted for by the fact that one is health state evaluation by patients and the other is for a hypothetical state by a group who have not experienced a fracture. As Brazier and colleagues[241] suggest, there were also differences in the state being valued, since the hypothetical state did not describe any particular type of fracture but included a discussion of future risk, whereas own health was valued using an anchor of best imaginable for age. According to Brazier and colleagues,[241] for economic models, a conceptually better approach to valuing established osteoporosis is to base it on the worst fracture experienced by the patient.

Hip fracture

Eighteen out of 24 different hip fracture values in *Table 201* across six studies report preference-based values appropriate for economic evaluation. These range from 0.28 to 0.91. The lowest values of 0.28 and 0.31 were for condition-specific states, but the health states descriptions were very different: life after a 'disabling'[233] and 'good'[235] hip fracture. Both were elicited using TTO, with the former anchored against best imaginable and the latter a good health state typical for their age. Adjusting for these anchors would increase the values to some extent.

The HUI-II valuation found in Gabriel[233] for those who had a hip fracture in the past 5 years was 0.68, compared with the TTO own HSUV of 0.70. The HUI-II evaluation found by Cranney and colleagues[242] was 0.67 and 0.71 at baseline and 2 months' follow-up, respectively.

TTO social tariff values applied to EQ-5D are also available from the study conducted in Malmö[231,243] at different points of time (2 weeks, 6 months, 12 months and 24 months). The health state at 2 weeks was 0.42. HSUVs increased at 6, 9 and 12 months.

Murray and colleagues[216] collected HSUVs using TTO-weighted EQ-5D before and after hip fracture in a population recruited into a clinical trial. This prospective data set offers a more valid estimate of the loss in health status associated with a hip fracture. The mean HSUVs at baseline, 6, 12 and 24 months after hip fracture were 0.54, 0.45, 0.45 and 0.5, respectively. These figures are lower than those reported by Gabriel and colleagues[233] for the HUI-II, and this could be due to the use of TTO rather than standard gamble and/or the fact that the population is significantly older. A key finding was that patients had a significantly lower HSUV (i.e. 0.54) compared with the average for their age (0.731).[215] The study by Murray and colleagues[216] is the only one that distinguishes between HSUV at 12 and 24 months after fracture.

Higher estimates were achieved for own health valuations by standard gamble evaluation.[242] Values were 0.91 and 0.84 at baseline and 2 months after the fracture, respectively.

As noted by Brazier and colleagues,[241] these results support the usual findings that patients give higher valuations than non-patients and that an explicit description of a state seems to elicit lower values.

Nursing home

There is only one published estimate for hip fracture cases in a nursing home,[235] but it was inappropriate for the model. Therefore, the NOF assumption of 0.4 was used.

Vertebral fracture

The empirical estimates for vertebral fracture were considerably below the NOF assumption of 0.97. The lowest values were obtained from non-fracture respondents[233] (0.31) for a hypothetical state of 'multiple' fractures and from patients respondents 2 weeks after the fracture occurred (0.21).[243]

The EQ-5D data from the study by Oleksik and colleagues[217] found evidence of a relationship between number of fractures and HSUV. Thoracic fractures had lower values than fractures located at the lumbar spine. TTO own health values[232,244] were not higher than the HUI value found in Gabriel[233] and Cranney[242] again possibly owing to the different valuation technique, but were higher than the estimates in Oleksik[217] based on a general population TTO valuation of the EQ-5D and the social tariffs applied to EQ-5D found in Johnell.[243] The value of 0.31 was obtained from non-fracture respondents for a hypothetical state of 'multiple' fractures. It may be seen that once again, an explicit description of the condition has resulted in a lower value than the generic descriptions.

After allowing for the expected HSUV in the age groups prone to vertebral fracture, the apparent difference to the NOF assumption is considerably reduced for some of the estimates. The HUI-II estimate for those who had a fracture in the past 5 years was 0.8, for example, compared with the normative value based on Canadian data of 0.82 for a comparable age group. The study by Oleksik and colleagues[217] produced values of 0.66–0.81 compared with general population norm of 0.81. One concern with these studies is that they recruited patients who had a fracture up to 5 years ago. There are no HSUV estimates against time of fracture and hence no separate estimates for year 1 and subsequent years. Furthermore, these studies used cross-sectional controls. The control cases in the study by Oleksik and colleagues[217] were patients who met the same inclusion criteria of age and *T*-score (<–2.5), but the authors found that the controls were significantly younger (by 2.5 years), had a higher lumbar spinal BMD and had a lower prevalence of non-vertebral fractures. The consequences of these differences for EQ-5D score before fracture (or as would have pertained if the fracture had not occurred) are not known.

The other value of 0.21 was obtained from the Malmö study from a sample of patients completing EQ-5D 2 weeks after the fracture. The Malmö study seems to present unique figures, as they do not match the values for vertebral fracture found in the current review. They are much lower (0.21, 0.49, 0.51 and 0.57 at 2 weeks, 6 months, 9 months and 12 months, respectively) than in the other studies presented and they are only comparable to the values found for hip fracture. The main problem with this study is that there were too many dropouts, with a sample that declined very rapidly period by period. The group of patients at 12 months comprised fewer then half of the patients who originally entered the study and was very small in absolute terms (12 patients compared with 40 at baseline). This implies that there are differences among the original sample (the one that originally entered the study) and the sample at 12 months. This study was regarded as too small and potentially unrepresentative to use in the model.

The selected value used in the model is from Oleksik[217] but, unlike for hip and wrist, this study was not been able to distinguish between the multiplier in the first year and subsequent years. This leads to the circumstance where any vertebral fracture following a first vertebral fracture will not have any impact on utility. This is unlikely to be correct, and may introduce bias against products that affect the risk of vertebral fractures. To reduce the effect of this problem it has been assumed that a similar proportion of disutility in the first and subsequent years to that seen in hip fracture will be experienced (utility year 1, 0.83; year 2, 0.925).[216] These multipliers were weighted so that the average multiplier value is 0.909, as reported in the Oleksik paper.[217] This study recruited patients who had suffered a clinical vertebral fracture within the preceding 5 years. An assumption was made about the number of people in the Oleksik study who had suffered a vertebral fracture within the past year. In the absence of other data it was assumed that patients were spread equally across the years and that 20% of patients would have suffered a vertebral fracture within 1 year. This would imply that 20% of patients would have a multiplier of x and the remaining 80% of patients a multiplier of $x(0.925/0.83)$. These would have an average of 0.909.

Thus, $0.2x + 0.8\ [x(0.925/0.83)] = 0.909$
Therefore, $1.09157x = 0.909$
Hence, $x = 0.83$, which is the assumed multiplier for year 1; for subsequent years it is 0.93.

Wrist fracture

Some earlier economic evaluations assumed that a wrist fracture has no impact on health status. The NOF model had values of 0.96 for year 1 and 0.98 for subsequent years for long-term dependency in a small proportion of cases. The first empirical study in the field found a significant impact over short periods.[218] The researchers administered the EQ-5D at admission and at the final visit to the accident and emergency department and estimated a mean loss in health state value over this period from the wrist fracture by assuming a linear progression between the first and last visit. A concern with this estimate is whether the EQ-5D would be sensitive to some of the problems associated with wrist fracture, particularly the longer term complications found in a small proportion of patients.

Lower estimates are available from Cranney[242] and Johnell.[243] The values found by Cranney and colleagues estimated with HUI-II were 0.67 at baseline and 0.71 2 months later. The problem with this study is that the sample was very small (only ten patients). The values derived by Johnell and colleagues were also lower (both the EQ-5D and VAS values), but they suffered from the same problems in the design of the study referred to previously for vertebral fracture.

Proximal humerus

On the advice of the clinical collaborators on this project it was assumed that a fracture of the proximal humerus has the same impact on health status as a wrist fracture.

Breast cancer

Several studies have presented empirically derived estimates of the impact of breast cancer on HSUV. The HSUV depends on whether the disease is stable or progressive, whether it is being treated and its stage. There is no average value for this disease and hence it was necessary to select one value that broadly represents the consequences of breast cancer for a person's health status. It was decided to choose the value for stable disease estimated by Hutton and colleagues.[219]

Coronary heart disease

This disease also suffers from the problem of being associated with more than one condition. There are estimates for patients following myocardial infarction and others have values for different severities of angina. The assumption of 0.85 was used in the model, with a range of 0.72–0.99 depending on the type of CHD and the methods of study.

Final selection of HSUVs for use in the model

There was a wide range of preference-based HSUVs for each condition, primarily owing to differences in the descriptive systems and the sample of respondents used in the valuation. One recommended solution in such a situation is to have a reference case of values for all analysts to use. This does not imply that analysts should only use the reference case in future economic evaluations, but the values should be used in at least one analysis of each economic evaluation of an intervention for osteoporosis.

The influential Washington Panel on Cost-Effectiveness recommends the use of a generic instrument with social valuations of health states obtained using a preference-based instrument.[211] This allows comparison between healthcare programmes, such as cardiac or cancer versus osteoporosis, as well as within programme. The problem to date with the condition-specific approach has been that this has been limited to one or two vignettes, and these do not necessarily reflect the full range of states associated with each condition. Furthermore, they cannot be easily linked to patients in trials. Generic instruments can be administered to patients in trials or other clinical studies and hence provide a more accurate quantitative basis to the descriptive results. Accepting that there may be problems with generic health state classifications for some conditions, such as insensitivity to the consequences of wrist fracture, another approach would be to produce a preference-weighted condition-specific measure.

This review found two generic preference-based measures being used, the EQ-5D and the HUI-II. There are few data on their relative performance in osteoporosis and there is no methodological basis for preferring one to the other. Currently, the EQ-5D has the advantage of being available for more osteoporosis-related conditions than the HUI-II and hence is preferred for the reference case set of values. In most cases a distinction was made between the first and subsequent year, as done by the NOF. The final selection of HSUVs used in the model is shown in *Table 64* in the main report (see Chapter 4).

The HSUVs found in this review do not cover all possible age groups. Some studies are limited to one age group and others are based on small numbers and it has not been possible to estimate reliable age-specific values. To extrapolate the findings from these studies to specific age groups, one approach would be to assume a constant absolute reduction regardless of age. Another is to assume a constant proportional effect on HSUVs. There is no evidence to support one assumption or the other. The latter approach was used for the reference case data set, since it assumes that the better a person's health status the more he or she has to lose, and this was thought to be the most realistic assumption. *Table 64* presents the multipliers for the proportionate effect of a fracture on HSUVs in the first year. For hip fractures, for example, the mean HSUV at 12 months is divided by the baseline value (0.45/0.54= 0.833). The 95% confidence intervals were estimated for each multiplier from the studies using Fieller's theorem.

There are many uncertainties surrounding the appropriate estimates to use in the model, for the reasons given above. The point estimates were used in the economic analyses, as they are unbiased estimators. It is recommended that further primary research is undertaken to try to obtain the true value of the multipliers associated with osteoporotic fractures

Appendix 15

Sensitivity analyses

Effects of including morphometric vertebral fractures that do not come to clinical attention

The issue of whether to include morphometric fractures that do not come to clinical attention is not clear cut, as there may be no direct medical costs and the QALY impact (if any) is unknown. To investigate whether incorporating these fractures would greatly affect the cost per QALY ratios, an extra analysis was undertaken using alendronate as a representative intervention. It was assumed that:

- one-third of morphometric fractures come to clinical attention[24]
- the cost of a morphometric fracture is comparable to that of a clinical fracture
- the utility loss is one-third of that of a clinical fracture, as assumed in the raloxifene submission.[39]

The impact of including morphometric fractures that do not come to clinical attention, in addition to those that do, was modelled by trebling the cost of a vertebral fracture and increasing the loss in utility by 66%, while keeping the incidence constant.

This equated to multipliers following a vertebral fracture of 0.78 in the first year and 0.88 in subsequent years. These changes are very extreme, particularly in regard to the utility loss associated with morphometric fractures that do not come to clinical attention, which have been assumed to have zero utility loss in the main analysis. The illustrative results are given in *Table 202*.

The inclusion of morphometric fractures did not markedly change the marginal QALYs gained but, as expected, the cost-effectiveness of the intervention was reduced.

Effects of assuming a greater utility loss in the first year following a vertebral fracture

The appraisal team's estimate of utility loss in the year of a vertebral fracture was 0.83. A number of submissions used a value of 0.63 following work undertaken in Malmö,[243] which was not deemed robust by the appraisal team. However, sensitivity analyses using alendronate as an illustrative example were conducted to show the impact of this variable on the final cost-effectiveness results (*Table 203*).

TABLE 202 *Effect of incorporating morphometric vertebral fractures using Alendronate (results given for a cohort of 100 women)*

Age (years)	Marginal cost per QALY (£)[a]	Marginal cost per QALY (£)[a]
50	33,621	30,676
60	39,733	37,195
70	16,934	16,516
80	697	675

[a] Compared with no treatment.

TABLE 203 *Effect of assuming a utility multiplier of 0.63 in the year of a vertebral fracture, rather than 0.83*

Age (years)	Marginal cost per QALY (£)[a]	Marginal cost per QALY (£)[a]
50	33,621	30,789
60	39,733	38,294
70	16,934	16,276
80	697	695

[a] Compared with no treatment.

TABLE 204 *Effect of assuming a fall time of 1 year using alendronate (results given for a cohort of 100 women)*

Age (years)	Marginal cost per QALY (£)[a]	Marginal cost per QALY (£)[a]
50	33,621	45,863
60	39,733	52,697
70	16,934	23,145
80	697	3,620

[a] Compared with no treatment.

TABLE 205 *Average cost per QALY for alendronate compared with no treatment, at different levels of compliance*

	Cost per QALY at each age			
Compliance level	50 years	60 years	70 years	80 years
100%	£33,621	£39,733	£16,934	£697
90%	£33,809	£39,972	£17,083	£826
80%	£34,045	£40,271	£17,269	£987
70%	£34,349	£40,656	£17,509	£1,194
60%	£34,753	£41,169	£17,828	£1,470
50%	£35,319	£41,887	£18,276	£1,857
40%	£36,169	£42,965	£18,947	£2,437
30%	£37,585	£44,761	£20,065	£3,403
20%	£40,416	£48,352	£22,301	£5,335
10%	£48,910	£59,126	£29,009	£11,132
5%	£65,898	£80,674	£42,425	£22,727
1%	£201,804	£253,061	£149,758	£115,481

The increase in year 1 disutility following a vertebral fracture reduces the cost per QALY ratio of the drug; however, the effect is not marked.

Effects of altering the assumed fall time of interventions

On clinical advice it has been assumed that the fall time should be set at 5 years. An analysis was undertaken, using alendronate as a representative drug, to evaluate the effects of reducing the fall time from 5 years to 1 year. These results are given in *Table 204*.

A reduction in the assumed fall time greatly increases the cost per QALY. Based on clinical advice it is unlikely that the interventions analysed have a fall time of only 1 year; however, this analysis provides some indication of the likely impact were this to be the case.

Evaluating the effects of reduced compliance levels

The effect of varying the compliance level (from the assumed 100% level) on the cost-effectiveness ratio was explored.

It was assumed that non-compliance would result in the cost of 3 months of the intervention with no health benefit gained. *Table 205* shows how the cost-effectiveness ratio changes for alendronate with changing levels of compliance for women at the threshold of osteoporosis and with a previous fracture.

The cost-effectiveness of alendronate for women at the threshold of osteoporosis and with a previous fracture at 70 and 80 years is robust until very low compliance levels (< 10%) are assumed. For the case of doubled fracture risk the cost-effectiveness of alendronate at all ages is robust until compliance falls below 5%. For women without a previous fracture the cost-effectiveness of raloxifene at 70 years is robust until compliance falls below 30% and the cost-effectiveness of alendronate at 80 years is robust until compliance falls below 20%.

Appendix 16

Comparing the results from the submission models and the appraisal model

This appendix analyses the base-case results provided in the submissions and discusses the key reasons why the results estimated by the appraisal model may produce different answers.

Alendronate

Comparability of populations analysed

The appraisal team evaluated interventions assuming that a woman was 50, 60, 70 or 80 years of age and had a *T*-score of –2.5 SD. The base case in the submission assumed that the age of a woman was 71 years for the prior fracture analysis and 69 years for the analyses assuming no previous fractures. The *T*-score assumed for women with prior fracture was –2.4 SD. This value was not specified for women with no prior fracture, but is estimated to be close to –2.1 SD.

Comparability of the assumed efficacy of alendronate

The mean efficacy data assumed by the appraisal team, and by the submission model,[42] are given in *Table 206*. These data are broadly comparable for patients with a prior fracture, although the differences become greater for patients without prior fractures. The submission model used data only from one trial the Fracture Intervention Trial,[98,99] compared with the meta-analysis undertaken by the appraisal team.

Comparability of costs associated with osteoporotic fractures

The costs used by the submission team and the appraisal team were very similar, except for the cost of a hip fracture. The submission team assumed that a set percentage of patients enters a nursing home following a hip fracture, and that this percentage is independent of age or prior residential status. This assumption is likely to overestimate greatly the cost of hip fracture in patients who are relatively young.

Comparability of the assumed disutility associated with osteoporotic fractures

Both models used multipliers to calculate the disutility associated with fracture and both allowed this multiplier to take values in year 1 different to those assumed in subsequent years. *Table 207* compares the values used in the appraisal model and the submission model.

Comparability of the fracture rates used

The submission model did not adjust the average population rate and assumed that this rate is applicable to patients with the average BMD at that age, and without prior fractures. This adjustment would have reduced the incidence of hip fracture, vertebral fracture and wrist fracture by 43%, 31% and 23%, respectively, and would have increased markedly the cost per QALY ratio

TABLE 206 *Comparing the efficacy data assumed for alendronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Relative risk used in the appraisal model for patients with prior fracture	0.53	0.46	0.48	1.00
Relative risk used in the submission model for patients with prior fracture	0.46	0.49	0.52	1.00
Relative risk used in the appraisal model for patients without prior fracture	0.56	0.62	0.64	0.87
Relative risk used in the submission model for patients without prior fracture	1.00	0.44	1.00	1.00

[a] Only fractures that come to clinical attention.

TABLE 207 *Comparing the efficacy data assumed for alendronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Utility multiplier assumed in the appraisal model in the initial year	0.830	0.830	0.981	0.981
Utility multiplier assumed in the submission model in the initial year	0.626	0.792	0.977	NA
Utility multiplier assumed in the appraisal model in subsequent years	0.930	0.925	1.000	1.000
Utility multiplier assumed in the submission model in the subsequent years	0.929	0.900	1.000	NA

[a] Only fractures that come to clinical attention.

for alendronate. The rationale for this reduction is detailed in Chapter 2 of the main report.

Comparing the baseline cost per QALY ratios

The baseline cost per QALY from the submission was £3135 for women with a prior vertebral fracture and aged 71 years, and £8622 for women with no prior fracture and aged 69 years. The assumed *T*-scores for women in both these groups were less than the threshold for osteoporosis.

The estimated cost per QALY for women with a *T*-score at the threshold for osteoporosis and aged 70 years was £9776 for women with a prior fracture and £34,403 for women without a prior fracture.

The appraisal model had cost-effectiveness ratios larger than those of the submission model. The key factor in this is the reduced fracture incidence assumed in the appraisal model, although focusing only on patients with a prior vertebral fracture will also reduce the cost-effectiveness ratio.

Risedronate

Comparability of populations analysed

The appraisal team evaluated interventions assuming that a woman was 50, 60, 70 or 80 years of age and had a *T*-score of –2.5 SD. The base case in the submission used women aged 70 years, with a risk of hip, vertebral and wrist fractures three times that of the average population. Assuming no increased risk, the risk of a hip fracture three times that of the average population would be equated with a *Z*-score of –1.74, which would equal a *T*-score of –3.3 SD at 70 years of age. With a prior fracture (that is assumed to double the risk of hip fracture) the *T*-score would fall to –2.56 SD. Thus, the submission model analysed a more severe population than the appraisal model.

Comparability of the assumed efficacy of risedronate

The submission for risedronate[43] contained two economic models. Only the model presented in the main report will be analysed, as the second model, by Kanis and co-workers,[43] produced results closer to those of the appraisal model. The mean efficacy data assumed by the appraisal team, and by the submission model,[43] are given in *Table 208*; neither model assumed that risedronate affected the probability of proximal humerus fracture. The submission model did not distinguish between patients with and those without prior fractures.

Comparability of costs associated with osteoporotic fractures

The costs used by the submission team and the appraisal team were very similar, except for the cost of a hip fracture. The submission team assumed that a set percentage of patients enters a nursing home following a hip fracture, and that this percentage is independent of age or prior residential status. This assumption is likely to overestimate greatly the cost of hip fracture in patients who are relatively young.

Comparability of the assumed disutility associated with osteoporotic fractures

The submission model used absolute disutility values to calculate the impact of fractures on quality of life, whereas the appraisal model used multipliers. For comparison purposes, the disutility values were transformed into multipliers at 70 years of age (where the average QALY score is 0.747).

TABLE 208 *Comparing the efficacy data assumed for risedronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist
Relative risk used in the appraisal model for patients with prior fracture	0.63	0.60	0.68
Relative risk used in the appraisal model for patients without prior fracture	0.63	0.66	0.68
Relative risk used in the submission model	0.69	0.60	0.80

[a] Only fractures that come to clinical attention.

TABLE 209 *Comparing the efficacy data assumed for risedronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Utility multiplier assumed by the appraisal team in the initial year	0.830	0.830	0.981	0.981
Utility multiplier assumed by the submission team in the initial year	0.906	0.172	0.976	NA
Utility multiplier assumed by the appraisal team in subsequent years	0.930	0.925	1.000	1.000
Utility multiplier assumed by the submission team in the subsequent years	1.000	0.773	1.000	NA

[a] Only fractures that come to clinical attention.

Table 209 compares the values used in the appraisal model and the submission model. There is great disparity in the values assumed for the disutility for hip fracture, particularly in the first year, with the submission model favouring the intervention.

Comparability of the fracture rates used

The submission model did not adjust the average population rate and assumed that this rate is applicable to patients with the average BMD at that age, and without prior fractures. This adjustment would have reduced the incidence of hip fracture, vertebral fracture and wrist fracture by 43%, 31% and 23%, respectively, and would have increased markedly the cost per QALY ratio for risedronate. The rationale for this reduction is detailed in Chapter 2 of the main report. The submission model also assumed that a greater number of morphometric fractures impacts on quality of life than the appraisal model.

Comparing the baseline cost per QALY ratios

The baseline cost per QALY from the submission was £577 for women aged 70 years with a risk of fracture three times that of the average population. With a prior fracture, a *T*-score of –2.56 SD would equate to a risk of hip fracture three times that of the average population.

The appraisal model evaluated the cost-effectiveness of risedronate in women with a prior fracture with a *T*-score of –2.5 SD. The cost per QALY in this analysis was £15,000.

The appraisal model had cost-effectiveness ratios larger than those of the submission model. The key factors in this are the reduced fracture incidence assumed in the appraisal model, the very large assumed disutility following hip fracture and the more severe population analysed in the submission model.

Etidronate

Comparability of populations analysed

The appraisal team evaluated interventions assuming that a woman was 50, 60, 70 or 80 years of age and had a *T*-score of –2.5 SD. The base case in the submission used women aged 70 years with a *T*-score of –2.5 SD, so the populations are directly comparable.

Comparability of the assumed efficacy of etidronate

The mean efficacy data assumed by the appraisal team, and by the submission model,[38] are given in *Table 210*; neither model assumed that etidronate affected the probability of proximal humerus

TABLE 210 *Comparing the efficacy data assumed for etidronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist
Relative risk used in the appraisal model for patients with prior fracture	0.40	1.00	1.00
Relative risk used in the appraisal model for patients with prior fracture for sensitivity analyses	0.40	0.85	0.92
Relative risk used in the submission model	0.61	0.85	0.92

[a] Only fractures that come to clinical attention.

TABLE 211 *Comparing the efficacy data assumed for etidronate by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Utility multiplier assumed by the appraisal team in the initial year	0.830	0.830	0.981	0.981
Utility multiplier assumed by the submission team in the initial year	0.906	0.172	0.976	NA
Utility multiplier assumed by the appraisal team in subsequent years	0.930	0.925	1.000	1.000
Utility multiplier assumed by the submission team in the subsequent years	1.000	0.773	1.000	NA

[a] Only fractures that come to clinical attention.

fracture, and neither model distinguished between efficacy data in patients with or without prior fractures. There is disparity in the vertebral fracture efficacy and also in efficacy estimates in hip and wrist fractures, where the submission model used epidemiological data to estimate efficacy data.

Comparability of costs associated with osteoporotic fractures

The costs used by the submission team and the appraisal team were very similar, except for the cost of a hip fracture. The submission team assumed that a set percentage of patients enters a nursing home following a hip fracture, and that this percentage is independent of age or prior residential status. This assumption is likely to overestimate greatly the cost of hip fracture in patients who are relatively young.

Comparability of the assumed disutility associated with osteoporotic fractures

The submission model used absolute disutility values to calculate the impact of fractures on quality of life, whereas the appraisal model used multipliers. For comparison purposes, the disutility values were transformed into multipliers at 70 years of age (where the average QALY score is 0.747).

Table 211 compares the values used in the appraisal model and the submission model. There is great disparity in the values assumed for the disutility for hip fracture, particularly in the first year, with the submission model favouring the intervention.

Comparability of the fracture rates used

The submission model did not adjust the average population rate and assumed that this rate is applicable to patients with the average BMD at that age, and without prior fractures. This adjustment would have reduced the incidence of hip fracture, vertebral fracture and wrist fracture by 43%, 31% and 23%, respectively, and would have increased markedly the cost per QALY ratio for etidronate. The rationale for this reduction is detailed in Chapter 2 of the main report. The submission model also assumed that a greater number of morphometric fractures impacts on quality of life than the appraisal model.

Comparing the baseline cost per QALY ratios

The baseline cost per QALY from the submission was £18,634 for women aged 70 years with a *T*-score of –2.5 SD.

TABLE 212 *Comparing the efficacy data assumed for raloxifene by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Breast cancer
Relative risk used in the appraisal model for patients with prior fracture[b]	0.65	1	1	0.42
Relative risk used in the appraisal model for patients without prior fracture[b]	0.53	1	1	0.42
Relative risk used in the submission model for patients with prior fracture	[CIC removed]	[CIC removed]	[CIC removed]	[CIC removed]

[a] Only fractures that come to clinical attention.
[b] Analyses were also run using a mean of 1.12 for hip fracture and 0.89 for wrist fracture.
CIC, commercial in confidence.

The appraisal model evaluated the cost-effectiveness of etidronate in 70-year-old women with a prior fracture with a *T*-score of –2.5 SD. The cost per QALY in this analysis was £28,329. An additional analysis was performed at 70 years of age assuming the efficacy used in the submission model. In this scenario the cost per QALY was approximately £20,000.

The appraisal model had cost-effectiveness ratios slightly larger than those of the submission model. The main factors in this are the reduced fracture incidence assumed in the appraisal model and the very large assumed disutility following hip fracture assumed in the submission model. The difference in the results is less for etidronate than for risedronate owing to the assumed lower efficacy of etidronate.

The efficacy data assumed by the submission model lower the cost per QALY relative to the efficacy data assumed in the appraisal model.

Raloxifene

Comparability of populations analysed

The appraisal team evaluated interventions assuming that a woman was 50, 60, 70 or 80 years of age and had a *T*-score of –2.5 SD. The submission provided data for combinations of ages and relative risks of vertebral fracture compared with the general population. The base-case analysis was in women aged 67 years, with relative risks of vertebral fracture, compared with the average population, of 1, 1.5 and 3. At 70 years of age, the appraisal model had a relative risk of vertebral fracture of 1.2 compared with the general population. This figure can be doubled for women with a previous fracture.

Comparability of the assumed efficacy of raloxifene

The mean efficacy data assumed by the appraisal team, and by the submission model,[39] are given in *Table 212*. The submission model did not distinguish between efficacy in patients with and without prior fracture.

These data are broadly comparable for patients with a prior fracture, although the differences become greater for patients without prior fractures. The difference in efficacies regarding breast cancer may balance out as the appraisal model used the figure for all breast cancer incidents, whereas the submission model used data on invasive breast cancer, of which there would be fewer cases. The submission model also includes morphometric vertebral fractures that do not come to clinical attention.

Comparability of costs associated with osteoporotic fractures and breast cancer

The costs used by the submission team and the appraisal team were very similar, except for the cost of a hip fracture. The submission team assumed that a set percentage of patients enters a nursing home following a hip fracture, and that this percentage is independent of age or prior residential status. This assumption is likely to overestimate greatly the cost of hip fracture in patients who are relatively young. However, if it is assumed that raloxifene has no effect on hip fractures this should not affect the results.

Comparability of the assumed disutility associated with osteoporotic fractures

Both models used multipliers to calculate the disutility associated with fracture and both allowed this multiplier to take values in year 1 different to

TABLE 213 *Comparing the efficacy data assumed for raloxifene by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus	Breast cancer
Utility multiplier assumed in the appraisal model in the initial year	0.830	0.830	0.981	0.981	0.62
Utility multiplier assumed in the submission model in the initial year	0.626	0.792	0.977	NA	0.9
Utility multiplier assumed in the appraisal model in subsequent years	0.930	0.925	1.000	1.000	0.62
Utility multiplier assumed in the submission model in the subsequent years	0.902	0.900	1.000	NA	0.9

[a] Only fractures that come to clinical attention.

those assumed in subsequent years. *Table 213* compares the values used in the appraisal model and the submission model. There is a significant difference in the assumed disutility following a breast cancer incident.

Comparability of the fracture rates used

The submission model did not adjust the average population rate and assumed that this rate is applicable to patients with the average BMD at that age, and without prior fractures. This adjustment would have reduced the incidence of hip fracture, vertebral fracture and wrist fracture by 43%, 31% and 23%, respectively, and would have increased markedly the cost per QALY ratio for raloxifene. The rationale for this reduction is detailed in Chapter 2 of the main report. The rate of breast cancer mortality derived in the submission model was calculated from standard breast cancer mortality rates. This may introduce bias into the calculations, as these data do not consider the length of time that a person may live from diagnosis of breast caner until death from this event.

Comparing the baseline cost per QALY ratios

The baseline cost per QALY from the submission was approximately £15,000 for women aged 67 years, regardless of whether the relative risk of vertebral fracture was 1 or 3.

The estimated cost per QALY for women aged 70 years and with a relative risk of vertebral fracture of 1.2 was £29,713, and was £23,671 for women with a relative risk of vertebral fracture of 2.4 (assumed due to a prior fracture). The appraisal model had cost-effectiveness ratios larger than those of the submission model. The key factors in this are the reduced incidences of both fracture and breast cancer assumed in the appraisal model. The relative insensitivity of the results to the relative risk of vertebral fracture demonstrates again that the key component in the magnitude of the cost-effectiveness ratio is the breast cancer effect. It is again reiterated that neither model is likely to be an accurate model of the condition of breast cancer and that these results should be treated with caution.

Teriparatide

Comparability of populations analysed

The appraisal team evaluated interventions assuming that a woman was 50, 60, 70 or 80 years of age and had a *T*-score of –2.5 SD. The base case in the submission model[40] used women aged 69 years with a relative risk of fracture, compared with the average population of just under 4.

Comparability of the assumed efficacy of teriparatide

The mean efficacy data assumed by the appraisal team, and by the submission model,[39] are given in *Table 214*. The submission model assumed that teriparatide did not affect the probability of proximal humerus fracture. Neither model distinguished between efficacy data in patients with or without prior fractures. Although the mean efficacy data are comparable, there was a marked difference in the approach of calculations, as the submission model used data from all non-vertebral fractures to populate hip and wrist fracture efficacy. The submission model also did not look at the confidence interval around these efficacy data, which was very large (0.09 to 2.73) for hip fracture in the appraisal model. The efficacy of teriparatide on hip fracture has yet to be proven

TABLE 214 *Comparing the efficacy data assumed for teriparatide by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Relative risk used in the appraisal model for patients with prior fracture[b]	0.35	0.50	0.54	0.80
Relative risk used in the submission model	0.35	0.47	0.47	1.00

[a] Only fractures that come to clinical attention.
[b] An additional analysis was conducted assuming no effect on hip, wrist and proximal humerus fractures

TABLE 215 *Comparing the efficacy data assumed for teriparatide by the appraisal team and the submission team*

	Vertebral[a]	Hip	Wrist	Proximal humerus
Utility multiplier assumed by the appraisal team in the initial year	0.830	0.830	0.981	0.981
Utility multiplier assumed by the submission team in the initial year	0.626	0.792	0.870	NA
Utility multiplier assumed by the appraisal team in subsequent years	0.930	0.925	1.000	1.000
Utility multiplier assumed by the submission team in the subsequent years	0.929	0.900	1.000	NA

[a] Only fractures that come to clinical attention.

and a separate analysis was run assuming no effect at the hip, wrist or proximal humerus.

The model treated the length of effect of Teriparatide favourably. It was assumed that treatment would have the full effect for a 5-year period with a fall time of 1 year. The submission model assumed full effect for 3 years, with a fall time of 3.5 years.

Comparability of costs associated with osteoporotic fractures

The costs used by the submission team and the appraisal team were very similar, except for the cost of a hip fracture. The submission team assumed that a set percentage of patients enters a nursing home following a hip fracture, and that this percentage is independent of age or prior residential status. This assumption is likely to overestimate greatly the cost of hip fracture in patients who are relatively young.

Comparability of the assumed disutility associated with osteoporotic fractures

The submission model used absolute disutility values to calculate the impact of fractures on quality of life, whereas the appraisal model used multipliers. For comparison purposes, the disutility values were transformed into multipliers at 70 years of age (where the average QALY score is 0.747).

Table 215 compares the values used in the appraisal model and the submission model. There is a great disparity in the values assumed for the disutility for hip fracture, particularly in the first year, with the submission model favouring the intervention.

Comparability of the fracture rates used

The submission model did not adjust the average population rate and assumed that this rate is applicable to patients with the average BMD at that age, and without prior fractures. This adjustment would have reduced the incidence of hip fracture, vertebral fracture and wrist fracture by 43%, 31% and 23%, respectively, and would have increased markedly the cost per QALY ratio for teriparatide. The rationale for this reduction is detailed in Chapter 2 of the main report.

Comparing the baseline cost per QALY ratios

The baseline cost per QALY from the appraisal model was £54,928 for women aged 70 years, with a prior fracture and a *T*-Score of –2.5 SD, when Teriparatide was assumed to cost £2000 per

annum. This figure fell to £23,941 when the risk of all fractures was doubled. When a cost of £3500 per annum was assumed these figures rose to £100,922 and £47,572, respectively. When the fracture risks were doubled the relative risk for hip fracture in women with a prior hip fracture compared with the average population was approximately 5.6. This value was 4.8 for women with a prior vertebral fracture.

[*Commercial-in-confidence information removed.*]

The cost per QALY ratio would also be increased in the appraisal model owing to the wide confidence intervals, which are of log-normal distribution. When the sampled efficacy is greater than 1 the increase in the number of hip fractures is greater proportionately than the savings made when the sampled number is below 1. As an example, assuming an expected number of 100 hip fractures the greatest reduction will be 100 when the relative risk is 0; however, if the confidence interval for relative risk also includes 2.5, then there are expected to be an additional 250 hip fractures. Thus, where confidence intervals span unity, the sampled number of expected hip fractures will be greater than the mean relative risk multiplied by the expected number of hip fractures.

The submission model did not analyse a scenario where teriparatide has no effect on hip fracture. If this were the case then the costs per QALY for this intervention would become very high (>£100,000).

Conclusions on which model should be used to assess the cost-effectiveness of osteoporosis interventions

SHEMO was constructed using an individual patient methodology, which is believed to produce more accurate results than a cohort method (see Appendix 12). This approach was also undertaken in the model of teriparatide,[40] and in the submission model of alendronate,[42] where it is stated that the difference between a cohort method and an individual is small.

If it is assumed that the differences in the methodologies can be ignored, then the main divergence between the models will be that of assumed costs and assumed QALYs of fracture events. The data used in the appraisal model have been discussed fully in the report; the costs did not differ substantially from those used in the submissions, except for hip fracture costs, where the submissions assumed that a constant percentage of women (7%) will enter a nursing home following a hip fracture, regardless of age. From data found to populate the appraisal model, this assumption appears to be incorrect, particularly in women aged 50 and 60 years.

The utilities used within the submissions are comparable to those used in the appraisal model. The main values that are different are in the first year following a vertebral fracture, where submissions[39,40,42] used data from a small sample of patients from Malmö,[243] and in hip fracture, where submissions[38] used estimates from the NOF, rather than empirical data estimates.

All models except for that for teriparatide[40] can be run using efficacy data randomly sampled from the confidence intervals. This is crucial in evaluating the current osteoporosis interventions, where a good deal of uncertainty remains in the true efficacy values.

The appraisal model is slightly conservative in that the costs and QALY adjustments associated with fractures, breast cancer and CHD events are curtailed at the end of the 10-year modelling horizon, with only the loss in QALYs associated with patients who die being considered beyond this point. For patients at younger ages the appraisal model will overestimate the cost per QALY ratio were costs and QALY adjustments to persist beyond the 10-year modelling horizon.

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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