Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

Final Protocol 4 September 2014

1. Title of the project:

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

2. Name of TAR team and 'lead'

TAR team

School of Health and Related Research Technology Assessment Group,

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Project lead

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3. Plain English Summary

Osteoporosis is a disease characterised by low bone mass (BMD) and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (a broken bone resulting from a fall at standing height or less). Fractures cause significant pain, disability and loss of independence and can be fatal.[1] Osteoporosis affects over three million people in the UK.[2] The UK has one of the highest rates of fracture in Europe, every year 300,000 people in the UK suffer a fragility fracture, including over 70,000 hip fractures.[3] In the UK, 1,150 people die every month following a hip fracture.[4] In 2002 the cost to the National Health Service per annum was estimated to be £1.7 billion, with the potential to increase to £2.1 billion by 2020, as estimated in 2005.[5] Whilst osteoporosis is an important predictor of the risk of fragility fracture, 70% of fragility fractures in postmenopausal women occur in those who do not meet the criteria for osteoporosis.[6]

4. Decision problem

4.1 Purpose of the decision to be made

This assessment will address the question "what is the clinical effectiveness and cost-effectiveness of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures as compared against each other or a non-active treatment?"

4.2 Clear definition of interventions

Four interventions will be considered within this assessment: alendronate, ibandronate, risedronate and zoledronate which are nitrogenous bisphosphonates. Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.[7]

(1) Alendronate (Fosamax, Fosamax Once Weekly and Fosavance [co-formulation with cholecalciferol], MSD) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once daily or weekly. It also has a UK marketing authorisation for treating osteoporosis in men and for preventing and treating corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy, orally once daily.[8]

Non-proprietary alendronate (AAH, Accord, Actavis, Alliance Healthcare, Almus, Apotex UK, Fannin UK, Focus, Generics UK, Kent, Mylan UK, Phoenix Healthcare Distribution, PLIVA, Ranbaxy, Rosemont, Somex, Sun, Teva UK, Waymade, Wockhardt and Zentiva) also has a UK marketing authorisation for the same indications.[8]

Alendronate in the treatment of postmenopausal osteoporosis is administered orally 10 mg daily or 70 mg once weekly. Treatment of osteoporosis in men is 10 mg daily. Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy is 10 mg daily. Treatment is administered while sitting or standing and patients should remain seated or stood for at least 30 minutes.[7]

(2) Ibandronate (Bonviva, Roche) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once monthly or every 3 months by intravenous injection. Non-proprietary ibandronate (Actavis UK, Consilient Health, Mylan UK, Sun and Teva UK) also has a UK marketing authorisation for the same indications[8].

Ibandronate in the treatment of postmenopausal osteoporosis is administered either by mouth 150 mg once a month or by intravenous injection over 15–30 seconds, 3 mg every 3 months. Oral treatment is administered while sitting or standing and patients should remain seated or stood for at least one hour.[7]

(3) Risedronate (Actonel and Actonel Once a Week, Warner Chilcott) has a UK marketing authorisation for treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, orally once daily or weekly. It has a marketing authorisation for preventing osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, orally once daily, and for treating osteoporosis in men at high risk of fractures, orally once weekly. Non-proprietary risedronate (AAH, Actavis, Alliance Healthcare, Aspire, Aurobindo, Bluefish, Dr Reddy's Laboratories, Mylan UK, Phoenix Healthcare Distribution, Ranbaxy, Sandoz, Sovereign Medical, Teva UK, and Zentiva) also has a UK marketing authorisation for the same indications[8].

Risedronate in the treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures is administered 5 mg daily or 35 mg once weekly. For the prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, administration is 5 mg daily. Treatment of osteoporosis in men at high risk of fractures is 35 mg once weekly. Patients should remain seated or stood for at least one hour after administration.[7]

(4) Zoledronate (Aclasta, Novartis) has a UK marketing authorisation for treating postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis in postmenopausal women and men) by intravenous infusion once a year. Zoledronate in the treatment of postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis in men and postmenopausal women) is administered by intravenous infusion, 5 mg over at least 15 minutes once a year. In patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair.[7] Non-proprietary zoledronate (SUN Pharmaceuticals) also has a UK marketing authorisation for the same indications.[9]

4.3 Place of the intervention in the treatment pathway(s)

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture and 3 technology appraisals of treatments for post-menopausal women only.

NICE technology appraisal guidance 160 (Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women),[10] recommends alendronate as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have an increased fracture risk defined by age, T-score, and number of independent clinical risk

factors for fracture, or indicators of low BMD. For women who cannot take alendronate, NICE technology appraisal guidance 160[10] and 204 (Denosumab for the prevention of osteoporotic fractures in postmenopausal women),[11] recommends risedronate, etidronate, strontium ranelate, teriparatide or denosumab, at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[8]

NICE technology appraisal guidance 161 (secondary prevention, in women who have already sustained a fracture), [12] recommends alendronate for secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. For women who cannot take alendronate, NICE technology appraisal guidance 161[12] recommends risedronate, etidronate, raloxifene, strontium ranelate, and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[8]

NICE technology appraisal guidance 204[11] recommends denosumab as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.[8]

People with osteoporosis who cannot tolerate oral therapies should be referred to secondary care for consideration of intravenous zoledronate or subcutaneous denosumab.

4.4 Relevant comparators

Bisphosphonates (alendronate, ibandronate, risedronate and zoledronate) may be compared against each other or a non-active agent, e.g., placebo.

Other bisphosphonates (e.g., etidronate) and other active agents (e.g., raloxifene, strontium ranelate, and teriparatide) will not be considered as comparators in this assessment.

Etidronate is not included as a comparator as it has been discontinued by the manufacturer in the UK. Non-bisphosphonates licensed for the prevention of fragility fractures in women and men will be considered in a separate MTA once this MTA on bisphosphonates has published its final appraisal determination

4.5 Population and relevant sub-groups

The assessment will consider adults assessed for risk of fragility fracture, according to the recommendations in NICE clinical guideline 146 as follows:

(1) All women aged 65 years and over.

(2) All men aged 75 years and over.

(3) Women aged 64 years and under in the presence of risk factors, for example:

- low BMD (a T-score of −1 standard deviations (SD) or more below the young adult mean) previously measured by DXA at the femoral hip,
- previous fragility fracture,
- current use or frequent recent use of oral or systemic glucocorticoids,
- history of falls,
- family history of hip fracture,
- other causes of secondary osteoporosis,
- low body mass index (BMI) (less than 18.5 kg/m^2),
- smoking,
- alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

(4) Men aged 74 years and under in the presence of risk factors (as specified in (3) for women aged 64 years and under).

4.6 Key factors to be addressed

The objectives of the assessment are to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared against (i) each other and (ii) no active treatment
- estimate the overall NHS budget impact in England and Wales

4.7 Factors that are outside the scope of the appraisal

An evaluation of the interventions in the following populations is outside of the appraisal scope and will not be considered in this assessment:

- Women aged 64 years and under without a risk factor (as listed under 4.5)
- Men aged 74 years and under without a risk factor (as listed under 4.5)

5. Methods for the synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'[13] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[14]

5.1. Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature relating to alendronate, ibandronate, risedronate and zoledronate within their licensed indications for the prevention of fragility fractures.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria below) and systematic reviews/meta-analyses (for the identification of additional trials). The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cochrane Database of Systematic Reviews (Wiley Interscience)
- Database of Abstract of Reviews of Effects (Wiley Interscience)
- Cochrane Central Register of Controlled Trials (Wiley Interscience)
- Health Technology Assessment Database (Wiley Interscience)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index Expanded (Web of Science)
- Conference Proceedings Citation Index - Science (Web of Science)
- BIOSIS (Web of Science)

Current research registers (e.g, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) will also be searched for ongoing and recently completed research projects. Citation searches of key included studies will also be undertaken using the Web of Science database.

Searches will not be restricted by language or publication type. Existing evidence reviews,[15] commissioned by NICE, which included literature published up to June 2008, will be assumed to have identified all papers relevant to this review published prior to 2008. Therefore searches will be limited by date from 2008 until present. The MEDLINE search strategy is presented in Appendix 1. High precision search filters designed to retrieve clinical trials and systematic reviews will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. Industry submissions and

relevant systematic reviews will also be hand-searched in order to identify any further relevant clinical trials. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

Inclusion criteria have been defined in line with the final scope provided by NICE and are outlined below.

5.2.1.1 Populations

(1) All women aged 65 years and over and men aged 75 years and over.

(2) Women aged 64 years and under and men aged 74 years and under in the presence of risk factors, for example: previous fragility fracture; current use or frequent recent use of oral or systemic glucocorticoids; history of falls; family history of hip fracture; other causes of secondary osteoporosis; low body mass index (BMI) (less than 18.5 kg/m^2); smoking, alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

(3) Women aged 64 years and under and men aged 74 years and under with low BMD (a T-score of −1 standard deviations (SD) or more below the young adult mean).

5.2.1.2 Interventions

Four interventions will be considered within this assessment: alendronate; ibandronate; risedronate and zoledronate.

5.2.1.3 Comparators

Interventions may be compared with each other. Interventions will also be compared with placebo or other non-active treatments (i.e., treatment without the potential to augment bone). Studies which administered calcium and / or vitamin D to patients in both the intervention and comparator arms will be included (e.g. bisphosphonate plus calcium vs. placebo plus calcium).

If studies comparing etidronate with one of the four bisphosphonate listed under 5.2.1.2 are identified, these studies and any studies comparing etidronate to placebo will be included in the review and used to inform the evidence network for the Bayesian meta-analysis.

5.2.1.4 Outcomes

The outcome measures to be considered include:

- fragility fracture
    - hip fracture
    - vertebral fracture (where data allow clinical/symptomatic fractures will be reported separately from morphometric/radiographic fractures. Radiographic /morphometric fractures will be defined as those resulting in a 20% or greater reduction in vertebral height)
    - all non-vertebral fracture
    - wrist fracture
    - proximal humerus fracture
    - fragility fracture at other sites
- bone mineral density at the femoral neck assessed by dual energy X-ray absorptiometry (DXA).
- mortality
    - all cause
    - mortality following hip fracture
    - mortality following vertebral fracture
    - mortality following fracture at site other than hip or vertebral
- adverse effects of treatment including but not limited to
    - upper gastrointestinal symptoms
    - osteonecrosis of the jaw
    - hypocalcaemia
    - bone pain
    - atypical femoral fractures
    - influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors
    - conjunctivitis
    - atrial fibrillation
    - stroke
- continuance and concordance (compliance)

- health-related quality of life
- healthcare resource use e.g., hospitalisation, entry into long-term residential care

5.2.1.5 Study design

Randomised controlled trials (RCTs) will be included in the clinical effectiveness systematic review. If no RCTs are identified for an intervention, non-randomised studies may be considered for inclusion. Non-randomised studies may also be included, where necessary, as a source of additional evidence (e.g., relating to adverse events, long-term incidence of fragility fracture, etc.) associated with the interventions.

5.2.2 Exclusion criteria

The following types of studies will be excluded:

- Studies in patients with normal or unspecified BMD who have not been selected based on the presence of risk factors
- Studies in patients with other indications for bisphosphonate treatment e.g Paget's disease, hypercalaemia of malignancy, metastatic breast cancer
- Studies where interventions are administered not in accordance with licensed indications
- Studies where interventions are co-administered with any other therapy with the potential to augment bone, unless concomitant treatments are specified in the summary of product characteristics
- Systematic reviews and clinical guidelines (these may be used as sources of references)
- Studies which are considered methodologically unsound in terms of study design or the method used to assess outcomes
- Studies which are only published in languages other than English
- Studies based on animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as abstracts or conference presentations only, where insufficient details are reported to allow an assessment of study quality or results.

5.2.3 Study selection

Retrieved studies will be selected for inclusion according to the inclusion and exclusion criteria specified in Sections 5.2.1 and 5.2.2. Studies will be assessed for relevance first by

title/abstract, and then finally by full text, excluding at each step studies which do not satisfy the inclusion criteria. One reviewer will examine titles and abstracts for inclusion, and a second reviewer will check at least 10% of citations. A kappa coefficient will be calculated to measure inter-rater reliability. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion and exclusion criteria.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form. A draft data extraction form is presented in Appendix 2. Data will be extracted with no blinding to authors or journal. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. A second reviewer will check at least 10% of data extraction forms. Discrepancies will be resolved by discussion. The Assessment Group's approach to handling data obtained from the manufacturers' submissions is detailed in Section 7.

Given the existence of previous NICE commissioned evidence reviews[15] in this area, if the number of new and previously reviewed studies identified for inclusion exceeds 30 we will restrict our data extraction to the new studies published since 2008 and will use the existing data reported in previous reviews[15] for studies published prior to 2008.

5.4 Quality assessment strategy

Methodological quality of RCTs identified for inclusion will be assessed using the Cochrane Collaboration risk of bias assessment criteria. This tool addresses specific domains, namely: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data and selective outcome reporting.

5.5. Methods of analysis/synthesis

Characteristics of included studies including population characteristics, intervention details, comparator details and outcomes will be tabulated and reported in a narrative synthesis.

For outcome measures about which there is interest in simultaneously comparing all treatments, a Bayesian random (treatment) effects network meta-analysis (NMA) will be undertaken, where data allow, using WinBUGS Version 1.4.3 (or OpenBUGS Version 3.2.3). Estimates and 95% credible intervals (CrIs) of the effects of bisphosphonates relative to the reference treatment (i.e. placebo) will be presented as will estimates and 95% CrIs for all pairwise comparisons. Evidence required to inform parameters in the economic model will be generated by taking draws from the posterior distribution i.e. CODA (Convergence

Diagnostic and Output Analysis). This will preserve the true underlying joint distribution and correlation structure of the treatment effects. The analysis and reporting will follow the principles outlined in Ades at al (2013).[16]

For other outcome measures of interest, Classical pairwise meta-analyses will be performed, where data allow, using Cochrane RevMan Version 5.2 or Stata Version 13.

5.6 Methods for estimating quality of life

Health-related quality of life (HRQoL) data reported by studies included in the clinical effectiveness systematic review will be extracted. In the absence of such evidence, the mathematical model may use evidence on HRQoL drawn from alternative sources.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

There exists a large number of published studies examining the cost-effectiveness of interventions to prevent fragility fracture. A recent systematic review by Müller *et a1*.[17] identified 24 studies published between 2006 and 2011 and two earlier reviews by Zethraeus *et al*.[18;19] identified 22 studies in the timeframe 1980-2001 and a further 22 studies published between 2002-2005. The estimates of cost-effectiveness from older published studies are unlikely to be directly applicable to the decision problem outlined in the scope due to the availability of generic bisphosphonates which has reduced the price of bisphosphonates over recent years. For example, alendronate at a dose of 10mg per day costs £301 per annum when using the once-daily branded product, but can be acquired for £10.92 per annum if choosing the weekly non-proprietary preparation. This comparison is based on current list prices[7] but a price of £301 per annum was also applied in the analysis published by Stevenson et al in 2005[20] which was conducted to inform TA160 and TA161. Therefore the TAR group will limit its searches for published economic evaluations to those published in 2006 or later.

A comprehensive search will be undertaken to systematically identify cost-effectiveness literature published in 2006 or later relating to alendronate, ibandronate, risedronate and zoledronate within their licensed indications for preventing fragility fractures in adults who are eligible for fracture risk assessment according to the recommendations in NICE clinical guideline 146.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index (ISI Web of Knowledge)
- Database of Abstract of Reviews of Effects (Wiley Interscience)
- Health Technology Assessment Database (Wiley Interscience)
- NHS Economic Evaluation Database
- EconLit (Ovid)
- BIOSIS (Web of Knowledge)

Citation searches of key included studies will also be undertaken using the Web of Science database.

Searches will not be restricted by language or publication type. Searches will be limited by date from the start of 2006 until present. The MEDLINE search strategy is presented in Appendix 9.1. High precision search filters designed to identify existing economic evaluations of bisphosphonates to prevent fragility fracture will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases as necessary. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Additional searches, for example to inform the decision-analytic model, where required in the course of the project, will be undertaken through consultation between the team.

Any existing health economic analyses identified by the searches will be critically appraised using the checklist published by Philips *et al.*[21] In addition, any economic analyses presented in the sponsor submissions to NICE will also be critically appraised using this checklist. Existing cost-effectiveness analyses may also be used to identify sources of evidence to inform structural assumptions and parameter values for the Assessment Group model.

6.2 Development of a *de novo* economic model

A *de novo* economic evaluation will be undertaken from the perspective of the UK NHS and Personal Social Services (PSS). The model will draw together evidence concerning treatment efficacy, continuance and compliance, treatment-related adverse events, resource use and HRQoL. Costs on drug acquisition, administration, hospitalisation, admission to long-term care, adverse events, primary care, and social care will be identified through literature searches and national formularies. In line with current recommendations, costs and health outcomes will be discounted at 3.5%. The primary health economic outcome of the model will be expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. The cost-effectiveness of all interventions and comparators will be compared incrementally against each other.

Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

The model will be used to identify treatment thresholds for each intervention. In order to identify treatment thresholds, a cost-effectiveness threshold will need to be assumed. A threshold of £20,000 per QALY will be used in the base case with an alternative threshold of £30,000 per QALY explored in a scenario analysis. All costs related to risk factors assessment including the use of DXA to assess BMD in patients close to a treatment threshold will be excluded from our analysis as these are already recommended by clinical guideline 146.

The thresholds for cost-effective treatment will be expressed using absolute fracture risk, as defined by either FRAX or QFracture, as these tools are recommended by clinical guideline 146 for the assessment of fracture risk. Previous work by the NICE Decision Support Unit[22] suggests that there are limitations to generating an algorithm to robustly predict the cost-effectiveness of interventions based only on absolute fracture risk (defined by either FRAX or QFracture). This is because there are many different ways to achieve a single level of risk using different combinations of patient characteristics (e.g age, gender, BMD, risk factors) and the cost-effectiveness of treatment is expected to vary according to the exact combination of characteristics. Depending on the availability of epidemiological data, the TAR team may need to employ pragmatic approaches and simplifying assumptions to estimate the average cost-effectiveness of treating individuals at a particular level of absolute risk.

7. Handling the company submission(s)

Data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 12 December 2014. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on economic model submission, will be assessed for clinical validity, reasonableness of assumptions, and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

None

9. Appendices

Appendix 9.1: Search strategy in Medline

1. exp osteoporosis/
2. osteoporo$.tw.
3. bone diseases, metabolic/
4. exp Bone Density/
5. (bone adj3 densit$).tw.
6. exp fractures, bone/
7. fractures, cartilage/
8. fracture$.ti,ab.
9. bone$ adj2 fragil$.tw.
10. bone mineral densit$.tw.
11. bone loss.tw.
12. bmd.tw.
13. or/1-12

14. (alendron$ or fosomax or fosavance).mp.
15. 121268-17-5.rn.
16. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
17. 114084-78-5.rn.
18. (risedron$ or actonel or atelvia or benet).mp.
19. 105462-24-6.rn.
20. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
21. 118072-93-8.rn.
22. or/14-21
23. 13 and 22

RCT filter for Medline (Ovid)

1. Randomized controlled trials as Topic/
2. Randomized controlled trial/
3. Random allocation/
4. randomized controlled trial.pt.
5. Double blind method/
6. Single blind method/
7. Clinical trial/
8. exp Clinical Trials as Topic/
9. controlled clinical trial.pt.
10. clinical trial$.pt.
11. multicenter study.pt.
12. or/1-11
13. (clinic$ adj25 trial$).ti,ab.
14. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
15. Placebos/
16. Placebo$.tw.
17. (allocated adj2 random).tw.
18. or/13-17
19. 12 or 18
20. Case report.tw.
21. Letter/
22. Historical article/
23. 20 or 21 or 22
24. exp Animals/

25. Humans/
26. 24 not (24 and 25)
27. 23 or 26
28. 19 not 27

Systematic review filter for Medline (Ovid)

1. meta-analysis as topic/
2. (meta analy$ or metaanaly$).tw.
3. Meta-Analysis/
4. (systematic adj (review$1 or overview$1)).tw.
5. "Review Literature as Topic"/
6. or/1-5
7. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
8. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
9. ((selection adj criteria) or (data adj extraction)).ab.
10. "review"/
11. 9 and 10
12. comment/ or editorial/ or letter/
13. Animals/
14. Humans/
15. 13 not (13 and 14)
16. 12 or 15
17. 6 or 7 or 8 or 11
18. 17 not 16

Economic search filter for Medline (Ovid)

1. exp "costs and cost analysis"/
2. economics/
3. exp economics, hospital/
4. exp economics, medical/
5. economics, nursing/
6. exp models, economic/
7. economics, pharmaceutical/
8. exp "fees and charges"/

9. exp budgets/
10. budget$.tw
11. ec.fs
12. cost$.ti
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti
15. (price$ or pricing$).tw
16. (financial or finance or finances or financed).tw
17. (fee or fees).tw
18. (value adj2 (money or monetary)).tw
19. quality-adjusted life years/
20. (qaly or qalys).af.
21. (quality adjusted life year or quality adjusted life years).af.
22. or/1-21

Appendix 9.2. Draft data extraction form

DRAFT DATA EXTRACTION FORM (VERSION 1.1)	
TRIAL DETAILS	
Author, year	
Country of corresponding author	
Trial name/number	
RCT design (e.g. multicentre, Phase I, Phase II)	
Geographical Setting (number of study sites, geographical location details)	
Publication type (i.e. full report or abstract)	
Sources of funding	
Inclusion/exclusion criteria	
Primary outcome/secondary outcomes	
No. recruited	
No. randomised	
Date of study	
INTERVENTIONS	
Intervention name	
Intervention class, dosing regimen and route of administration	
Comparator name	
Comparator dosing regimen and route of administration	
Treatment setting	

Duration of treatment	
Length of follow-up (if different)	
OUTCOME ASSESSMENT	
Radiographic assessment of femoral neck BMD (model and manufacturer of DXA machine)	
Fracture assessment, e.g., clinical/radiological assessment, time assessed	
Adverse event reporting	
Continuance and concordance reporting	
Quality of life instrument	
NHS and PSS resource use reporting	
POPULATION CHARACTERISTICS	
Numbers randomised to treatment groups	
Age	
Gender	
Ethnicity	
Height and weight	
Extent of disease severity at baseline, e.g., osteoporosis, osteopenia, or normal BMD	
Number of years post menopause (women)	
Comorbidities at baseline	
Details of any previous fractures	
Any details of previous conventional treatments (including type, dose and duration)	
Proportion receiving other treatments at baseline	
Details of any other medication at baseline and whether discontinued	
Concomitant medications during study	
History of: previous fragility fracture, glucocorticosteroid use, falls, family history of hip fracture, low BMI, smoking and alcohol use, secondary osteoporosis	
Any other relevant information	
Were intervention and control groups comparable?	
ANALYSIS	
Statistical techniques used	
Intention to treat description and methods for handling missing data	
Power calculation	
METHODOLOGICAL QUALITY ASSESSMENT	
Method of random sequence generation	
Method of allocation concealment	
Blinding of participants and caregivers	

Blinding of outcome assessment	
Attrition	
Selective reporting	
OUTCOMES	
Numbers completing	
Reasons for withdrawal	
RESULTS	
BMD at the femoral neck	
Fracture rates	
Adverse events	
Continuance and concordance	
Health-related quality of life	
Mortality	
Rates of hospitalisation due to fracture	
Rates of new admission to long-term residential care	
Other information	
SUMMARY	
Authors' overall conclusions	
Reviewers' comments	

Appendix 9.3. Timetable/milestones

Milestone	**Date**
Draft protocol	22 August 2014
Final protocol	05 September 2014
Progress report	19th December 2014
Draft assessment report	27 February 2015
Final Assessment report	27 March 2015

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