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

Final Protocol 8th August 2018

1. Title of the project:

Non-bisphosphonates for the prevention of osteoporotic fragility fractures (ID901)

2. Name of TAR team and 'lead'

TAR team

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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 abaloparatide, denosumab, raloxifene, romosozumab and teriparatide, within their licensed indications, for the prevention of osteoporotic fragility fractures as compared against each other, bisphosphonates or a non-active treatment?"

4.2 Clear definition of interventions

Five interventions will be considered within this assessment: abaloparatide, denosumab raloxifene, romosozumab and teriparatide.

(1) Abaloparatide (Eladynos, Radius Health) is a synthetic peptide analogue of human parathyroid hormone-related protein that stimulates new bone formation. It is administered subcutaneously. Abaloparatide does not currently have a marketing authorisation in the UK for treating osteoporosis. It has been studied in clinical trials compared with placebo and compared with teriparatide for the prevention of fractures in postmenopausal women with severe osteoporosis.

(2) Denosumab (Prolia, Amgen) is a monoclonal antibody that reduces osteoclast activity, and so reduces bone breakdown. Denosumab has a marketing authorisation in the UK for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Denosumab is administered as a single subcutaneous injection, of 60mg in 1 ml, once every 6 months.

(3) Raloxifene (Evista, Daiichi Sankyo) is a selective oestrogen receptor modulator. Raloxifene has a marketing authorisation in the UK for the treatment and prevention of osteoporosis in postmenopausal women. Non-proprietary raloxifene (Sandoz, Consilient Health, Actavis UK, Mylan UK) is also available for the same indication. The use of raloxifene to prevent osteoporosis is outside of the scope of this appraisal. Raloxifene in the treatment of postmenopausal is administered orally at a dose of 60mg daily.

(4) Romosozumab (Evenity, UCB and Amgen) is a monoclonal antibody that inhibits the protein sclerostin, increasing bone formation and decreasing bone breakdown. It is administered as a subcutaneous injection. It does not currently have a marketing authorisation in the UK for treating osteoporosis. It has been studied in clinical trials as 12 months of romosozumab followed by at least 12 months of alendronic acid, compared with at least 24 months of alendronic acid alone, in postmenopausal women. It has also been studied in a randomised, placebo-controlled clinical trial for treating osteoporosis in men.

(5) Teriparatide (Forsteo, Eli Lilly) is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates formation of new bone and increases resistance to fracture. It is administered daily as a subcutaneous injection of 20 micrograms for up to 24 months. Teriparatide has a marketing authorisation in the UK for treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. It also has a marketing authorisation in the UK for treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. Biosimilar versions of teriparatide (Movymia, Internis Pharmaceuticals; Terrosa, Gedeon Richter) have been licensed for the same indications.

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 (CCG146)[7] , and four technology appraisals of treatments for the prevention of osteoporotic fractures.

NICE technology appraisal 464 (Bisphosphonates for treating osteoporosis)[8], provides guidance on the level of fracture risk at which oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) become cost-effective for the prevention of osteoporotic fragility fracture. The implementation section of TA464 states that the guidance should be applied in conjunction with the NICE Quality Standard on Osteoporosis (QS149) [9] which provides clinical intervention thresholds for bisphosphonates.

For postmenopausal women who have already sustained a clinically apparent fragility fracture, but who cannot take alendronic acid or risedronate sodium, NICE technology appraisal guidance 204 (Denosumab for the prevention of osteoporotic fractures in postmenopausal women)[10] recommends denosumab and NICE technology appraisal guidance 161 (Raloxifene and Teriparatide for the primary prevention of osteoporotic fragility fractures in postmenopausal women)[11] recommends raloxifene and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[8]

For postmenopausal women who have not already sustained a clinically apparent fracture, NICE technology appraisal 204 (Denosumab for the prevention of osteoporotic fractures in postmenopausal women),[10] recommends denosumab at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture, but NICE technology appraisal guidance 160 (Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women) states that raloxifene is not recommended. [12]

It should be noted that TA 161[11] specifically does not cover the use of teriparatide in the prevention of osteoporotic fragility fractures in women who are on long-term systemic glucocorticoid treatment and TA 160[12] and TA161[11] specifically do not cover the use of raloxifene for the prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia (that is, women with a T-score between −1 and −2.5 SD below peak BMD).

4.4 Relevant comparators

Non-bisphosphonates (abaloparatide, denosumab, raloxifene, romosozumab and teriparatide) may be compared against each other, against bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid) or against a non-active agent, e.g., placebo.

Etidronate is not included as a comparator as it has been discontinued by the manufacturer in the UK. Strontium ranelate is not included as a comparator as it is no longer marketed in the UK.

4.5 Population and relevant sub-groups

The assessment will consider adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146[7] as follows:

- In all women aged 65 years and over and all men aged 75 years and over
- in women aged under 65 years and men aged under 75 years 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 (as defined in CG146)[7]
  - low body mass index (BMI) (less than 18.5 kg/m2)
  - smoking
  - alcohol intake of more than 14 units per week for women and more than 21 units per week for men.
- people aged under 50 years who have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture)

Whilst CG146 recommends that BMD should not be routinely measured without prior assessment using FRAX (without a BMD value) or QFracture, it does recommend BMD measurement in specific groups.[7] Furthermore, the quality standard which provides recommendations on clinical treatment thresholds (QS149),[9] recommends that BMD is measured in patients with a 10-year fracture probability between the upper and lower assessment threshold. Any patient identified as having osteoporosis, defined as a BMD that lies 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of <-2.5 SD),[1] during risk factors assessment would be considered at risk of osteoporotic fragility fracture and therefore included within the scope.

Within this broad population of patients eligible for risk assessment, we will assess the clinical and cost-effectiveness of each treatment within its licensed population which will include the following groups;

- postmenopausal women with osteoporosis
- men at increased risk of fracture
- women at increased risk of fracture
- women with osteoporosis associated with glucocorticoid use
- men with osteoporosis associated with glucocorticoid use

If evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146)[7] or that affect the impact of fracture on lifetime costs and outcomes will be considered.

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, (ii) bisphosphonates and (iii) no active treatment

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) except where osteoporosis has been confirmed by DXA

- Men aged 74 years and under without a risk factor (as listed under 4.5) except where osteoporosis has been confirmed by DXA

For the purposes of this appraisal, bisphosphonates will be assumed to be given in accordance with the guidance in TA464[8] and QS149[9] and the cost-effectiveness of bisphosphonates compared no treatment will not be re-evaluated.

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 abaloparatide, denosumab, raloxifene, romosozumab, and teriparatide 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 Online Library)
- Database of Abstract of Reviews of Effects (Wiley Online Library)
- Cochrane Central Register of Controlled Trials (Wiley Online Library)
- Health Technology Assessment Database (Wiley Online Library)
- Science Citation Index Expanded (Web of Science)
- Conference Proceedings Citation Index - Science (Web of Science)

The 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. Searches will be limited by date from 2008 until present. Existing evidence reviews [15] commissioned by NICE, which included literature published up to June 2008, will be assumed to have identified all papers related to raloxifene and teriparatide published prior to 2008. Papers published prior to 2008 related to denosumab are assumed to have been identified during development of TA204. We assume that there will be no papers related to abaloparatide, or romosozumab published prior to 2008 as these would pre-date drug development. The searches conducted for TA464[8] will also be updated to identify any literature published since September 2014 related to the clinical effectiveness of alendronic acid, ibandronic acid, risedronate and zoledronic acid within their licensed indications for the prevention of osteoporotic fragility fractures. The MEDLINE search strategy is presented in Appendix 1. High sensitivity 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 EndNote bibliographic software (version X8, Clarivate analytics).

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

Adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146 (as per section 4.5), including those identified by DXA scan as having osteoporosis.

5.2.1.2 Interventions

Five interventions will be considered within this assessment: abaloparatide, denosumab raloxifene, romosozumab and teriparatide.

5.2.1.3 Comparators

Interventions may be compared with each other and with bisphosphonates (alendronic acid, risedronate sodium, ibandronic acid and zoledronic acid). 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. raloxifene plus calcium vs. placebo plus calcium).
The original network of bisphosphonate studies identified in TA464[8] and any new studies identified in the updated searches will be included in the Bayesian network meta-analysis to allow non-bisphosphonates to be compared directly or indirectly with bisphosphonates.

If evidence allows, treatment sequences including bone forming agents (abaloparatide, romosozumab and teriparatide) followed by anti-resorptives agents (bisphosphonates, denosumab and raloxifen) will be considered.

5.2.1.4 Outcomes

The outcome measures to be considered include:

- Osteoporotic 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 related to osteoporosis
- bone mineral density (BMD) at the femoral neck assessed by dual energy X-ray absorptiometry (DXA). [BMD measured at the lumbar spine will be considered only where data on BMD measured at the femoral neck are not available]
- mortality
    - all cause
    - mortality following hip fracture

    - mortality following vertebral fracture
    - mortality following fracture at a site other than hip or vertebral
- adverse effects of treatment including but not limited to
    - infections
    - sweating or hot flushes
    - muscle cramps
    - peripheral oedema
    - breast discomfort
    - headache or migraine
    - hypertension
    - rashes
    - dyspnoea
    - cytopenia
    - thrombophlebitis, thromboembolism or stroke
    - gastrointestinal symptoms including nausea, diarrhoea, constipation, reflux
    - osteonecrosis of the jaw or the external auditory canal
    - hypocalcaemia or hypercalcemia
    - hypophosphataemia
    - bone pain
    - atypical femoral fractures
    - influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors
    - eye disorders (conjunctivitis or cataracts)
    - atrial fibrillation
    - injection site reactions
    - hypersensitivity reactions
- 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 the same drugs e.g 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 with a

second reviewer checking 10% of sifted titles. 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 100% of extracted numerical data. 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, we will restrict our data extraction to new studies published since 2008 and will use the existing data reported in previous reviews[15] for studies published prior to 2008. The existing data extracted during TA464[8] will be used for studies comparing bisphosphonates to placebo or one bisphosphonates to another bisphosphonate, but this will be supplemented by any new data identified during the update search for bisphosphonates.

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, and where data allow, a random (treatment) effects network meta-analysis (NMA) will be undertaken. Where possible, explanations for heterogeneity between RCTs in treatment effects will be explored using meta-regression, including patient characteristics associated with fracture risk, as listed in Section 4.5., including the presence of osteoporosis identified on DXA scan.

Random effects models will be implemented in a Bayesian framework using the freely available software packages WinBUGS Version 1.4.3 (or OpenBUGS Version 3.2.3) and R.

Results will be summarised using point estimates and 95% credible intervals (CrIs) of the effect of each treatment relative to the reference treatment. Other summary measures may also be presented such as 95% CrIs for all pairwise comparisons and probabilities of treatment rankings. Evidence required to inform parameters in the economic model will be generated by taking draws from the posterior predictive distribution of a new study. This will preserve the true underlying joint distribution and correlation structure of the treatment effects. Absolute goodness-of fit will be assessed using residual deviance. Where possible, consistency between direct and indirect estimates of treatment effect in NMAs will be assessed.

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

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 economic 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

A comprehensive search will be undertaken to systematically identify cost-effectiveness literature relating to abaloparatide, denosumab, raloxifene, romosozumab and teriparatide within their licensed indications.

Studies examining the cost-effectiveness of bisphosphonates without comparing against one of the non-bisphosphonate interventions included in the scope are not considered relevant to this appraisal.

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)
- Database of Abstract of Reviews of Effects (CRD Database)
- Health Technology Assessment Database (CRD Database)
- NHS Economic Evaluation Database (CRD Database)

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 to those published since the start of 2006. This is because studies reporting cost-effectiveness estimates for raloxifene, denosumab and teriparatide, are assumed to have been captured in the searches and reviews that informed TA160, TA161 and TA204 and studies reporting the cost-effectiveness of abaloparatide and romosozumab are not expected prior to 2006. 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 EndNote bibliographic software (version X8, Clarivate analytics).

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.*[16] 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

In order to ensure consistency across related appraisals, the economic analysis conducted to inform TA464[8] is intended to be used as the starting point for any cost-effectiveness analysis conducted by the assessment group. The appropriateness of the existing assessment group model as a starting point for the decision problem considered in this appraisal will be critically assessed by the assessment group and if necessary the existing model will be amended or a new model will be developed.

The assessment group's 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 related to 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. Non-skeletal benefits of treatment, such as reductions in the risk of breast cancer, will be excluded from the model on the basis that it is outside of the scope of the decision problem to assess the optimal combination of treatments for people at risk of both osteoporosis and another condition, such as breast cancer. In line with current recommendations, costs and health outcomes will be discounted at 3.5% per annum. The primary health economic outcome of the model will be expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Where more than one intervention or comparator is considered to be a potential alternative treatment option within the same patient population, an incremental analysis will be conducted to determine the most cost-effective treatment option. As it is expected that the most cost-effective treatment option will vary depending on the risk of fracture, it will be necessary to conduct incremental analyses for subgroups of patients stratified by baseline risk.

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 within each subgroup of patients. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

The model will be used to identify thresholds for cost-effective intervention for each treatment within the subgroup of patients covered by its licensed indication. 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.

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 and have been used previously to determine the thresholds for cost-effective intervention in TA464.[8] In the modelling conducted for TA464, the version of FRAX with unknown BMD was used. However, the NICE quality standard that defines the thresholds for clinical intervention (QS149),[9] recommends that patients with a

FRAX score between the lower and upper assessment thresholds should be referred for BMD measurement and their fracture probability reassessed. We will therefore attempt to explore whether the thresholds for cost-effective intervention vary when using the version of FRAX with known BMD. However, in order to do this, it may be necessary to make simplifying assumptions regarding the relationship between BMD and the other risk factors incorporated within FRAX. All costs related to risk factor assessment including the use of DXA to assess BMD in patients between the lower and upper assessment thresholds will be excluded from our analysis as these are already recommended by CG146.[7]

7. Handling the company submission(s)

Data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 4th September 2018. 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*.tw.
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 (ibandron* or boniva or bondronat or bonviva or adronil).mp.
16 (risedron* or actonel or atelvia or benet).mp.
17 (zoledron* or zometa or zomera or aclasta or reclast).mp.
18 or/14-17
19 limit 18 to yr="2014 -Current"
20 (abaloparatide or eladynos).mp.
21 (denosumab or prolia or xgeva).mp.
22 (raloxifene or evista or keoxifene).mp.
23 (romosozumab or evenity).mp.
24 (teriparatide or forsteo or movymia or terrosa).mp.
25 or/20-24
26 13 and (19 or 25)

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 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	4th May 2018
Final protocol	25th May 2018
Progress report	11th September 2018
Draft assessment report	4th November 2018
Final Assessment report	4th December 2018

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