NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Medicines for treating osteoporosis and reducing the risk of fragility fractures (review of TA160, TA161, TA204, TA464, TA791 and TA991)

Draft scope

Draft remit and evaluation objective

To appraise the clinical and cost effectiveness of medicines to reduce the risk of fragility fractures and osteoporosis in adults, within their marketing authorisations and within the context of the update of NICE's guideline on osteoporosis. The multiple technology appraisal (MTA) will focus on men aged 50 and over and women who have experienced menopause and are eligible for pharmacological treatment.

Background

Osteoporosis is a progressive skeletal disorder which is characterised by low bone mass and deterioration of the structure of the bone, leading to an increase in bone fragility and risk of fracture.

Osteoporosis is asymptomatic and often remains undiagnosed in the absence of fracture. In the UK, it is estimated that around 3.8 million people have osteoporosis.[1] The prevalence of osteoporosis increases markedly with age. In women, decreased oestrogen levels after the menopause accelerate bone loss, increasing the risk of osteoporosis. Half of women and one-fifth of men over the age of 50 will break a bone, mostly as a result of osteoporosis.[2] Osteoporosis can also be caused by the long-term systemic use of glucocorticoids which are a type of corticosteroid. These are anti-inflammatory medicines used for a wide range of conditions including autoimmune diseases and allergies.

There are approximately 536,000 new fragility fractures in the UK per year,[3] of which about 345,000 happen in women.[4] Osteoporotic fragility fractures occur most commonly in the hip, vertebrae and wrist. After a hip fracture, a high proportion of people are permanently unable to walk independently or to perform other activities of daily living and, consequently, many are unable to live independently. Vertebral fractures can be associated with curvature of the spine and height loss, and can result in chronic pain, breathing difficulties, gastrointestinal problems and difficulties in performing activities of daily living. Both hip and vertebral fractures are associated with increased mortality.

There are a number of clinical tools and considerations used to assess the risk of fracture and osteoporosis. These inform treatment criteria and guide the point at which it is appropriate to start pharmacological treatment. They include a measure of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) scanning and associated T-score. A T-score relates to the measurement of BMD using hip and or spine DXA scanning and is expressed as the number of standard deviations from peak BMD. FRAX and Qfracture are risk assessment tools that are used to calculate the 10-year probability of hip and major osteoporotic fracture. These tools are often used in combination with consideration of risk factors such as age and hormone levels, as well as fracture history.

The aim of primary prevention is to prevent any fragility fractures for a group of people deemed at risk of fragility fracture. This tends to include women who have experienced menopause and men aged 50 and over. Secondary prevention is for those within this group who have had at least one fragility fracture and are at risk of further fragility fractures. Within both primary and secondary prevention there will be people at particularly high risk of fragility fracture. To date there have not been clear and unified thresholds used to determine treatment eligibility and initiation, or to define the subgroup of people deemed to be very high risk.

NICE is updating its clinical guideline osteoporosis risk assessment, treatment and prevention of fragility fractures. The guideline will update and replace the NICE guideline on assessing the risk of fragility fracture in osteoporosis (CG146) and will also extend it to cover treatment to reduce primary and secondary fracture risk. The guideline will be consulted on in two parts. Part one of the guideline update covers risk assessment up to and including determination of clinical appropriateness for treatment and is being consulted on in parallel with this scope. Recommendations on treatments to reduce primary and secondary fracture risk and treatment will be part of a second update after this MTA has concluded, and will contextualise the pharmacological treatments included in this MTA as well as recommendations for exercise, calcium and vitamin D supplementation and monitoring of treatment.

Part one of the guideline update produced guidance on eligibility criteria for initiation of pharmacological treatment for fragility fracture risk. At the same time, the guideline committee developed definitions to determine who would be considered at very high risk of fragility fracture. They also considered if there were any relevant subgroups. This was for the purpose of this MTA and resulted in four clinically relevant populations:

1. Primary prevention for men aged 50 and over and women who have experienced menopause and meet the criteria for pharmacological treatment (see 1, figure 1).

2. Primary prevention for men aged 50 and over and women who have experienced menopause and meet the very high risk criteria (see 2, figure 1)

3. Secondary prevention for men aged 50 and over and women who have experienced menopause and meet the criteria for pharmacological treatment (see 3, figure 2)

4. Secondary prevention for men aged 50 and over and women who have experienced menopause and meet the very high risk criteria (see 4, figure 2)

These populations are shown in figures 1 and 2. Figure 1 shows primary prevention and figure 2 shows secondary prevention.

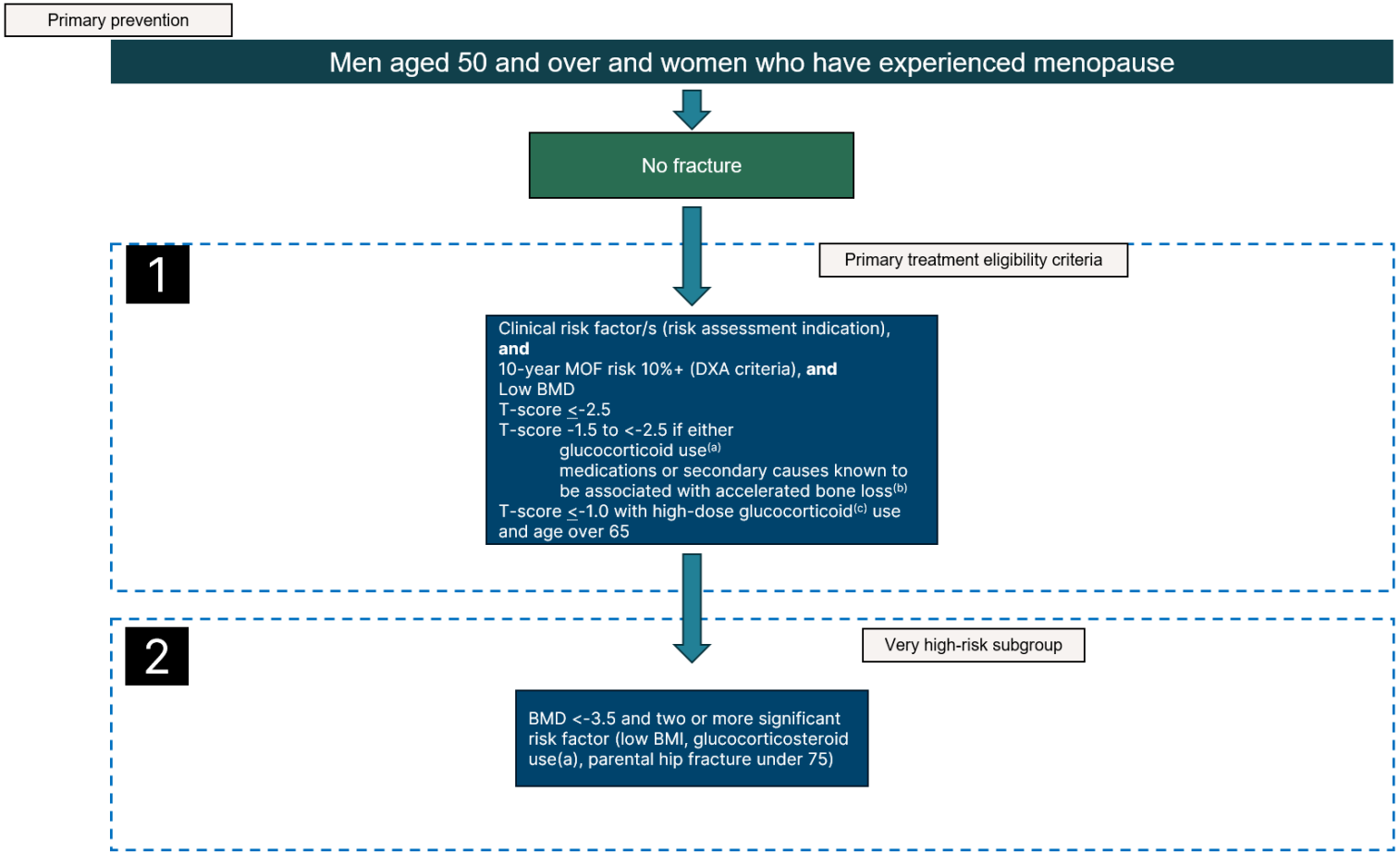
Other possible subgroups that could be explored if the evidence allows are:

- People with glucocorticoid-induced osteoporosis

- Women aged 50 to 60 years having hormone replacement therapy

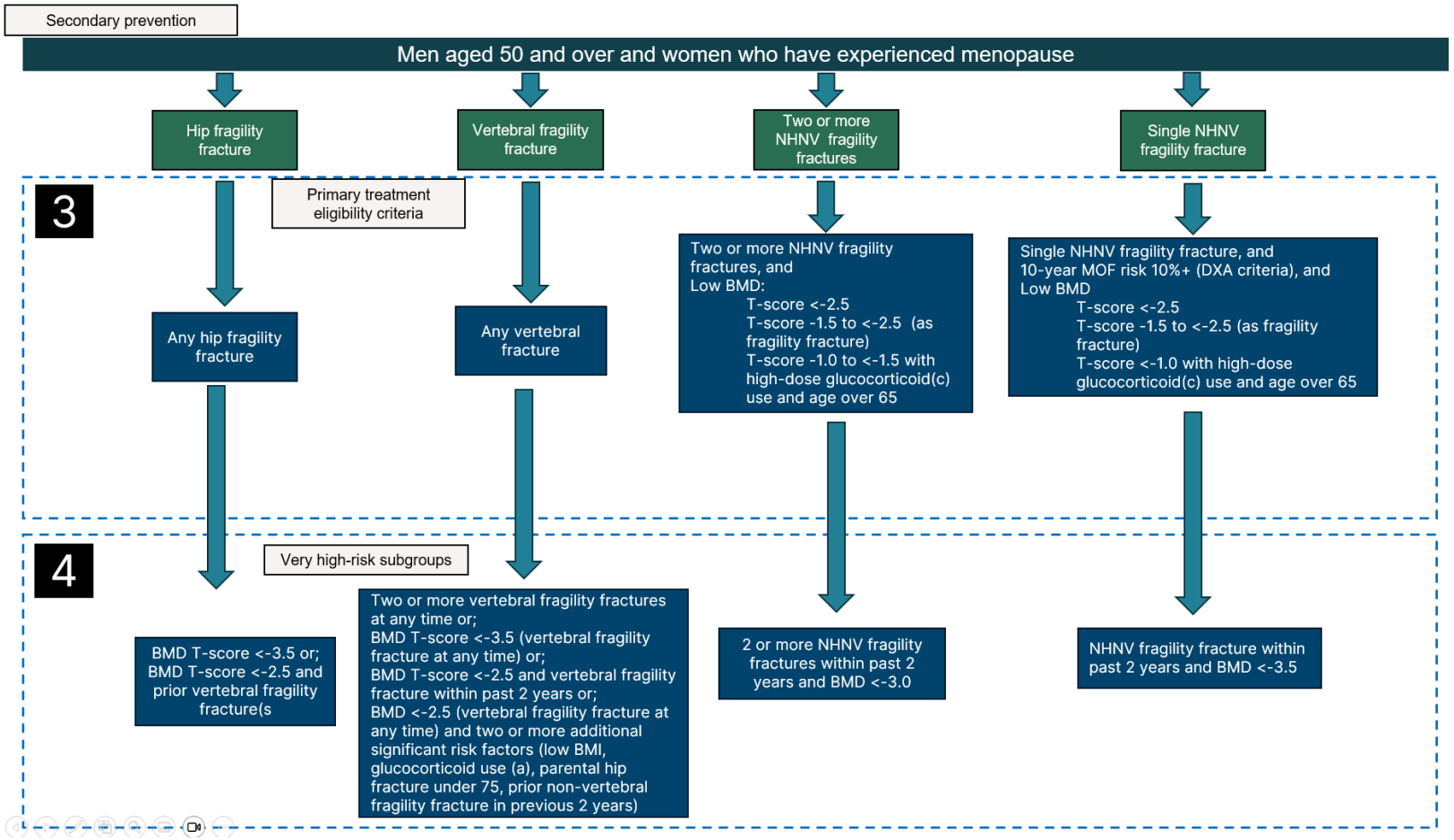
- People who are unable to take oral bisphosphonates because of cognitive difficulties or severe gastrointestinal side effects

Figure 1: The clinical definitions for risk of fragility fracture, including those at very high risk, for primary prevention of fragility fracture for men aged 50 and over and women who have experienced menopause



BMD, bone mineral density; BMI, body mass index; MOF, major osteoporotic fracture

Figure 2: The clinical definitions for risk of fragility fracture, including those at very high risk, for secondary prevention of fragility fracture for men aged 50 and over and women who have experienced menopause



BMD, bone mineral density; BMI, body mass index; MOF, major osteoporotic fracture; NHNV, non-hip non vertebral

The draft recommendations for risk assessment from part one of the guideline update are inconsistent with the methods of risk assessment that were used as treatment thresholds in the osteoporosis treatments that have been evaluated by NICE to date. In addition, the risk assessment criteria within the wording of each TA recommendation are not consistent with each other or updated clinical practice and require updating. This inconsistency in thresholds for suitability for pharmacological treatment, and who is deemed to be at high risk of fragility fracture needs to be resolved to produce recommendations that are useful, usable and align with the updated osteoporosis guideline. This MTA is being conducted to review the clinical and cost effectiveness of osteoporosis treatments currently recommended by NICE within the 4 populations recommended by the guideline committee.

Table 1 details the current NICE recommended technologies, their licensed indication and the existing NICE recommendation.

Table 2 shows the four populations of interest and which drugs are available for each population according to their marketing authorisation and existing NICE recommendation. We are seeking input through the consultation on which drugs are appropriate to consider for each population within this MTA.

Table 3 details the subgroups, outcomes and other details for consideration in the cost-effectiveness model.

Table 1: osteoporosis treatments with NICE recommendations, their marketing authorisations and NICE TA recommendations

Drug and NICE TA number	Marketing authorisation	NICE recommendation
Abaloparatide – NICE technology appraisal 991	Abaloparatide is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.	Abaloparatide is recommended as an option for treating osteoporosis after menopause in women, trans men and non-binary people if they have a very high risk of fracture as defined by the National Osteoporosis Guideline Group (NOGG) clinical guideline for the prevention and treatment of osteoporosis as a fracture probability (based on the Fracture Risk Assessment Tool [FRAX]) that exceeds the threshold for intervention by 60%.
Romosozumab – NICE technology appraisal 791	Romosozumab is indicated for the treatment of severe osteoporosis in	Romosozumab is recommended for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if they have had a major

	postmenopausal women at high risk of fracture.	osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture).
Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) – NICE technology appraisal 464 Alendronic acid is also known as alendronate and sodium alendronate. Ibandronic acid is also known as ibandronate and ibandronate sodium. Risedronate sodium is also known as risedronate and risedronic acid. Zoledronic acid is also known as zoledronate.	Alendronic acid is indicated in adults for the treatment of postmenopausal osteoporosis. Ibandronic acid is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Risedronate sodium is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures, for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures and prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. Zoledronic acid is indicated for the treatment of osteoporosis in postmenopausal women and adult men at increased risk of fracture, including those with a recent low-trauma hip fracture and for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in postmenopausal women	Oral bisphosphonates and intravenous bisphosphonates are recommended for treating osteoporosis in adults: • who are eligible for risk assessment as defined in NICE clinical guideline 146 and NICE's quality standard on osteoporosis • who are at higher risk of osteoporotic fragility fracture using the methods recommended in NICE CG 146 and QS on osteoporosis • taking into account their risk of fracture, adverse effects from bisphosphonates, and their clinical circumstances and preferences on osteoporosis, depending on the person's risk of fragility fracture. thresholds. This guidance partially updates NICE's technology appraisal guidance on raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160) and raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in

	and in adult men at increased risk of fracture.	postmenopausal women (TA161).
Denosumab – NICE technology appraisal 204	Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.	Denosumab is recommended for the primary 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 are contraindicated and • who have a combination of T-score, age and number of independent clinical risk factors for fracture Denosumab is recommended 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 are contraindicated For this recommendation the independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day and rheumatoid arthritis

Raloxifene and teriparatide – NICE technology appraisal 161 Raloxifene is also known as raloxifene hydrochloride.	Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women Teriparatide is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. Teriparatide is also indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture.	Raloxifene and teriparatide are recommended for the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have specified fracture risks defined by age, T-score and either number of independent clinical risk factors for fracture (for raloxifene) or number of fractures (for teriparatide). These recommendations are for women who have already sustained a fracture and who cannot take alendronate or risedronate.
Raloxifene – NICE technology appraisal 160	As above	Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

Table 2: Decision points, populations, licenced treatments and available technologies according to current NICE recommendations

Decision point	Populations	Available treatments according to licence	Available treatments according to NICE recommendations
1	Primary prevention, meet pharmacological treatment criteria	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • IV bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab • Raloxifene • Teriparatide	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • Intravenous bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab for those unable to take oral bisphosphonates (alendronate and risedronate) Not recommended: • Raloxifene is not recommended for primary prevention • Teriparatide is not recommended for primary prevention
2	Primary prevention, meet very high-risk definition	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • IV bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • Intravenous bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab for those unable to take oral bisphosphonates (alendronate and risedronate) • Abaloparatide Not recommended:

		• Raloxifene • Teriparatide • Abaloparatide • Romosuzumab	• Raloxifene is not recommended for primary prevention • Teriparatide is not recommended for primary prevention • Romosuzumab is not recommended for primary prevention
3	Secondary prevention, meet pharmacological treatment criteria	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • IV bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab • Raloxifene • Teriparatide • Abaloparatide • Romosuzumab	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • Intravenous bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab for those unable to take oral bisphosphonates (alendronate and risedronate) • Teriparatide for those unable to take oral bisphosphonates • Raloxifene for those unable to take oral bisphosphonates • Abaloparatide for those who have a very high risk of fracture as defined by the National Osteoporosis Guideline Group (NOGG) clinical guideline for the prevention and treatment of osteoporosis as a fracture probability (based on the Fracture Risk Assessment Tool [FRAX]) that exceeds the threshold for intervention by 60%. • Romosuzumab for those who have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture).

4	Secondary prevention, meet very high-risk definition	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • IV bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab • Raloxifene • Teriparatide • Abaloparatide • Romosuzumab	• Oral bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium) • Intravenous bisphosphonates (ibandronic acid, zoledronic acid) • Denosumab • Teriparatide • Raloxifene • Abaloparatide for those who have a very high risk of fracture as defined by the National Osteoporosis Guideline Group (NOGG) clinical guideline for the prevention and treatment of osteoporosis as a fracture probability (based on the Fracture Risk Assessment Tool [FRAX]) that exceeds the threshold for intervention by 60%. • Romosuzumab for those who have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture).

Table 3: Subgroups, outcomes and other details for consideration in the cost-effectiveness model

Subgroups	If evidence allows the following groups should be considered separately: • People with glucocorticoid-induced osteoporosis • Women aged between 50 and 60 years having hormone replacement therapy • People who are unable to take oral bisphosphonates because of cognitive difficulties or severe gastrointestinal side effects
Outcomes	The outcome measures to be considered include: • osteoporotic fragility fracture • bone mineral density • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
Related NICE recommendations	**Related technology appraisals:** Abaloparatide for treating osteoporosis after menopause (2024) NICE technology appraisal guidance 991 Romosozumab for treating severe osteoporosis (2022) NICE technology appraisal guidance 791. Bisphosphonates for treating osteoporosis (2017, updated 2019) NICE technology appraisal guidance 464.

	Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (2008, updated 2018) NICE technology appraisal guidance 161. Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women (2008, updated 2018) NICE technology appraisal guidance 160. Denosumab for the prevention of osteoporotic fractures in postmenopausal women (2010) NICE technology appraisal guidance 204. **Related NICE guidelines:** Osteoporosis: assessing the risk of fragility fracture (2012, updated 2017) NICE guideline CG146. **Related NICE guidelines in development:** Osteoporosis: risk assessment, treatment, and fragility fracture prevention (update). NICE guideline. Publication expected July 2026. **Related quality standards:** Osteoporosis (2017) NICE quality standard 149

Questions for consultation

In practice are oral bisphosphonates considered before intravenous bisphosphonates?

The following questions relate to specific populations:

Population 1:

Would it be appropriate to assess the cost effectiveness of raloxifene, teriparatide and denosumab for the primary prevention group (no fracture) that meet the primary treatment eligibility criteria?

Would it be appropriate to consider women aged over 65 years with BMD <-1 who do not meet the primary treatment eligibility criteria? Is this group covered within the marketing authorisations of the drugs?

The current NICE recommendation for denosumab specifies for those unable to take alendronate and risedronate. Would it be appropriate to amend this to ‘oral bisphosphonates’? This same question applies as relevant to the other populations.

Population 2:

Would it be appropriate to assess the cost effectiveness of raloxifene, teriparatide and romosuzumab for the primary prevention group (no fracture) that meet the definition for being at very high risk of fragility fracture?

Population 3:

In practice, which treatments are used for the secondary prevention group (previous fracture) who meet the primary treatment eligibility criteria?

Is it appropriate to assess the cost effectiveness of abaloparatide and romosuzumab within this group?

Would it be appropriate to consider women aged over 65 years with BMD <-1 who do not meet the secondary prevention treatment eligibility criteria? Particularly those with non-hip, non-vertebral fractures. Is this group covered within the marketing authorisations of the drugs?

Population 4:

In practice, which treatments are used for the secondary prevention group that meet the definition for being at very high risk of fragility fracture?

Would it be appropriate to include oral bisphosphonates, IV bisphosphonates, denosumab, teriparatide, raloxifene, abaloparatide and romosuzumab here?

Is it appropriate to consider HRT as a treatment option within this MTA?

For the following drugs, please select whether A, B, C or D applies:

A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care
D. Other (please give details):

- Oral bisphosphonates
- IV bisphosphonates
- Denosumab
- Teriparatide
- Raloxifene
- Abaloparatide
- Romosuzumab

Do you consider that the use of any of these drugs can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. Kanis J et al. (2021). SCOPE 2021: a new scorecard for osteoporosis in Europe. Archives of Osteoporosis 16 (82):

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3. Compston J et al. (2017) UK clinical guideline for the prevention and treatment of osteoporosis. Archives of Osteoporosis 12(1): 43

4. Svedbom, A et al. Osteoporosis in the European Union: a compendium of country-specific reports. Archives of Osteoporosis 8(1):137.