OSTEOPOROSIS GUIDELINE

- This guideline incorporates some of the recommendations from SIGN, NICE, National Osteoporosis Guideline Group (NOGG) and local expert opinion. It adopts a pragmatic approach to assess patients' risk of fracture in conjunction with the use of bone mineral density (BMD) measurement.

- The use of BMD has a high specificity but low sensitivity. This means that most osteoporotic fractures will occur in women who do not have osteoporosis as defined by a T-score of less than -2.5. Therefore clinical risk factors and/or BMD can be considered for treatment.

- Patients with clinical risk factors should be considered for fracture risk assessment using FRAX® tool. In the absence of BMD patients are categorised into having high, intermediate, or low fracture risks
  - Individuals with high risk are considered for treatment
  - Individuals with intermediate risk are considered for DXA and recalculation of the fracture risk.
  - Individuals with low risk are re-assessed in 5 years.

- Population screening for osteoporosis is not recommended. Do not routinely assess fracture risk in people under the age of 50 unless they have major risk factors (corticosteroid user, untreated premature menopause or previous fragility fracture) because they are unlikely to be at high risk.

- Patients who have sustained a clinically apparent osteoporotic fragility fracture will usually be reviewed by the Fracture Liaison service. A DXA scan may be arranged and clinical review offered. In other cases letters of advice are sent to the patients GP regarding treatment of osteoporosis.

- Osteoporosis may be assumed in women aged 75 years or older who have sustained fragility fracture if a DXA scan is considered to be clinically inappropriate or unfeasible. Local practice is that treatment rather than investigation with DXA benefits this patient group.

- Alendronic acid 70mg once weekly is the first-line treatment. Patients should comply with administration instructions to minimise oesophageal irritation.

- Information regarding bisphosphonate treatment length/treatment breaks can be found in a separate guidance.

- Updated to include NICE TA464 on bisphosphonate for treating osteoporosis updated July 2019.
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Definitions

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<tr>
<th>Osteoporosis</th>
<th>WHO: A bone mineral density (BMD) of 2.5 standard deviations (SD) or more below the mean peak mass of average of young healthy women, as measured by dual-energy X-ray absorptiometry (DXA). (Reported as a T-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia</td>
<td>As above with T-score between -1.0 SD and -2.5 SD</td>
</tr>
<tr>
<td>Fragility fracture</td>
<td>Fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level trauma (e.g. falling from a standing height or lower)</td>
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</table>

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>DXA (DEXA)</td>
<td>Dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>GNRH</td>
<td>Gonadotropin-releasing hormone</td>
</tr>
<tr>
<td>IBS</td>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>NOGG</td>
<td>National Osteoporosis Guideline Group</td>
</tr>
<tr>
<td>ONJ</td>
<td>Osteonecrosis of the jaw</td>
</tr>
<tr>
<td>PPIs</td>
<td>Proton Pump inhibitors</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic Lupus Erythematous</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Re-uptake Inhibitors</td>
</tr>
</tbody>
</table>
1. Adult Osteoporosis Treatment Pathway

**Fragility Fracture**

- Fracture Liaison Service (FLS)
- Perform fracture risk assessment, and if required, DXA, and review in clinic OR Write to GP advising treatment (Osteoporosis often assumed in women aged over 75 with fragility fracture where DXA inappropriate or unfeasible)
- Exclude non-osteoporotic causes and secondary osteoporosis

**Clinical Risk Factors** – Consider assessment of fracture risk in patients with significant risk factor or 3 other risk factors. Do not routinely test fracture risk in people under the age of 50 or premenopausal women (specialist advice should be sought)

**Significant risk factors:**
- History of fragility fracture
- Parental history of osteoporosis
- "Low BMI (<18.5kg/m²)
- ≥3 months oral corticosteroid use

**Other risk factors**
- Women aged >65 or Men >75
- "Smoking
- "Alcohol intake per week >14 units for women or >21 units for men
- Rheumatoid arthritis
- Diabetes
- Asthma
- Chronic liver disease
- Moderate to severe CKD (eGFR<60ml/min)
- Neurological diseases (alzheimers, parkinsons, stroke, MS)
- Inflammatory bowel disease
- Institutionalised patients with epilepsy
- Primary hyperparathyroidism and endocrine diseases
- Drug therapy: antiepileptics, pioglitazone, GnRH agonists, aromatase inhibitors, long term depotprogesterone acetate

* Modifiable risks- patients should be encouraged to achieve IBW, give up smoking & reduce alcohol intake.

**Calculate 10 year fracture risk using FRAX® tool**

- High risk
- Intermediate
- Low risk

**DXA & recalculate FRAX®**

If age-matched percentage <80% i.e. Z score <−2.0: exclude non-osteoporotic causes and causes of secondary osteoporosis (consider referral)

- High risk
- Low risk

Reassure reassess in 5 years or less depending on the clinical context

Management strategy should be made on an individual basis after informed discussion about risk and benefit. See NICE decision support tool. NICE TA464: oral bisphosphonates are options for treating osteoporosis in patients who have been assessed as being at higher risk of osteoporotic fragility fracture and when bisphosphonate treatment is appropriate, taking into account risk of fracture, risk of adverse effects from bisphosphonates, and clinical circumstances and preferences.

**Specialist referral**

Other treatment may be considered (denosumab, HRT, teriparatide, raloxifene, zoledronate)

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2. Risk assessment Tool

The use of BMD has a high specificity but low sensitivity. This means that most osteoporotic fractures will occur in women who do not have osteoporosis as defined by a T-score of less than -2.5. For this reason population screening is not recommended and risk factors listed above are considered.

NICE CG146 recommends assessing fracture risk but does not specify a tool (FRAX® or QFracture®). The FRAX® tool (www.shef.ac.uk/FRAX) is the preferred risk tool recommended by JAPC.

FRAX® tool was developed based on extensive data on multiple cohorts, and a version calibrated to fracture epidemiology in the UK is available. It computes the 10 year probability of hip fracture or a major osteoporotic fracture, and can be calculated with or without BMD. In absence of BMD NOGG recommends patients are categorised as having:
- High risk- patients with probability above the upper assessment threshold
- Intermediate risk- patients with probability between upper and lower assessment threshold
- Low risk- patients with probability below the lower assessment threshold

Interpret the estimated 10-year fracture risk with caution in people aged 80 years and over, as the short-term fracture risk may be underestimated.

The national osteoporosis society gives useful advice regarding repeating DXA scans. The decision as to whether and when to repeat a DXA scan depends on the initial results and the individual patient’s circumstances. However, it is rarely helpful to repeat DXA scans within 2 years.

3. Investigations for osteoporosis

Investigate and address if underlying causes are suspected as per detailed below. This is especially important in patients with vertebral fractures and in people with fragility fracture who are at low risk e.g. men, pre-menopausal women, women with premature menopause.

If no apparent cause found and severity of osteoporosis high (multiple fractures or significantly reduced bone density compared to that expected for age i.e. if age-match percentage <80%/ Z score <-2.0), referral to osteoporosis clinic may be appropriate for more thorough investigation. This is more likely to be the case for younger patients or men presenting with osteoporosis but the full detail of the case should be considered rather than having an age or sex based criteria for referral.

<table>
<thead>
<tr>
<th>Underlying Causes suspected</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption, malignancy, inflammatory disease</td>
<td>FBC, ESR, coeliac antibodies</td>
</tr>
<tr>
<td>Osteomalacia, hyperparathyroidism, bone metastases</td>
<td>Calcium, phosphate, Alk Phos, vitamin D</td>
</tr>
<tr>
<td>Liver disease</td>
<td>LFT</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>TSH</td>
</tr>
<tr>
<td>Male Hypogonadism</td>
<td>Testosterone, SHBG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of secondary osteoporosis</th>
<th>Non-osteoporotic causes &amp; features for fragility fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Endocrine conditions such as untreated premature menopause in women, hypogonadism in men, diabetes mellitus, hyperthyroidism, hyperprolactinaemia and Cushing’s disease.</td>
<td>• Metastatic bone disease - bone pain, history of cancer (especially lung, thyroid, prostate, kidney, or breast cancer), or symptoms of undiagnosed cancer (for example unexplained general malaise or weight loss).</td>
</tr>
<tr>
<td>• Rheumatological conditions such as rheumatoid arthritis, and other inflammatory arthropathies.</td>
<td>• Multiple myeloma - bone pain, anaemia, recurrent infections, bleeding, symptoms of hypercalcaemia, or kidney disease.</td>
</tr>
<tr>
<td>• Gastrointestinal conditions that cause malabsorption such as Crohn’s disease, ulcerative colitis, coeliac disease, and chronic pancreatitis.</td>
<td>• Osteomalacia - bone pain, muscle pain, or proximal muscle weakness.</td>
</tr>
<tr>
<td>• Chronic liver disease.</td>
<td>• Paget's disease - bone pain or deformity</td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease.</td>
<td></td>
</tr>
</tbody>
</table>

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4. Corticosteroid users

Patients on or commencing high dose oral corticosteroid long-term (7.5mg or more per day prednisolone or its equivalent for 3 months or more) should be offered bone protection with bisphosphonate. Patients taking lower doses of oral corticosteroid long-term should be considered for fracture-risk assessment. For patients starting on very high doses of steroids or a prolonged duration is anticipated, e.g. giant cell arteritis, it may be appropriate to commence bisphosphonates at the outset as significant bone loss occurs early on.

FRAX assumes an average dose of prednisolone and may underestimate fracture risk in patients taking higher doses, and overestimate risk in those taking lower doses. When the UK FRAX model is used and the glucocorticoid box is filled, 2 points appear on the NOGG graphs, one for 2.5-7.5mg daily of prednisolone or its equivalent, and one for ≥7.5mg daily of prednisolone.

Those aged 30-40 years of age who cannot be risk assessed using FRAX, and taking 7.5mg or more per day of oral prednisolone for 3 months or longer, require a BMD assessment using DXA. People under 30 would not yet have reached peak bone mass therefore DXA may not be appropriate.

5. Pharmaceutical management

**Bisphosphonates**

1st line: Alendronic acid 70mg once weekly

2nd line: Risedronate 35mg once weekly (may have better gastrointestinal tolerance)

An oral bisphosphonate is cost effective for treating osteoporosis in adults if the person is eligible for risk assessment on osteoporosis and the 10-year probability of osteoporotic fragility fracture is at least 1% (NICE TA 464). However, this does not mean that oral bisphosphonates should be routinely offered to all adults with a 10-year probability of osteoporotic fragility fracture of at least 1% alone. This is the risk level at which oral bisphosphonates are cost effective, and is not an intervention threshold. Decision on treatment should be made on an individual basis after an informed discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. (NNT at 1% risk is 200 for vertebral fractures and 333 for hip fractures) See NICE decision support tool and appendix 1.

Reflux and dyspepsia are common side-effects of alendronate. Patients presenting should be checked for concordance and asked to follow instructions – tablet to be taken whole on arising with full glass of water, at least half an hour before the first food or drink (except water) in the morning. Patients should not lie down or return to bed after taking the medication. PPIs should not be used to treat reflux type symptoms.

MHRA has issued guidance on the use and safety of bisphosphonate. Side effects and concerns:

- Atypical femoral fractures reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis (MHRA 2011 )
- Osteonecrosis of the jaw (ONJ) is a recognised complication of antiresorptive treatments- risk with oral bisphosphonates is low. Cancer patients should have a dental check-up before bisphosphonate treatment (MHRA 2009)
- Oral formulations with serious oesophageal adverse reactions
- Very rare reports of osteonecrosis of the external auditory canal (MHRA 2015)

Patients should be advised to:

- Stop taking the bisphosphonate and seek medical advice if they experience any signs or symptoms of possible oesophageal reaction, for example dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn.
- Have a regular dental check-up and to tell their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures;
- Report any pain in the thigh, hip, or groin, as ‘incomplete’ atypical femur fractures can occur, with some people experiencing pain weeks to months before presenting with a completed fracture

Alendronic acid 70mg effervescent tablets (Binosto) may be considered for patients with dysphagia/ long-term swallowing difficulties. Follow manufacturer’s administration direction. Patients should not swallow the undissolved effervescent tablet, should not chew the effervescent tablet or allow the effervescent tablet to dissolve in their mouths because of the risk for oropharyngeal irritation. Not to be used with thickening agent.
If an oral bisphosphonate is not tolerated or is contraindicated, consider specialist referral. Specialist treatment options include denosumab, HRT, teriparatide, raloxifene & zoledronic acid.

**Drug treatment holiday** (see JAPC local guidance)
Data suggests that the longer-term use of oral bisphosphonate treatment may be associated with increased risk of drug-related side effects, in particular, atypical femur fracture. It has been suggested that patients on oral bisphosphonates may benefit from ‘drug breaks’ following a spell on treatment (particularly after 5 or more years of use) in the hope that this may reduce the risk of skeletal adverse effects. If treatment is discontinued, fracture risk should be re-assessed after a new fracture; or if no new fractures, after 2 years.

**Calcium and vitamin D**
Combination treatment (Calcium + Vitamin D)
Patients should aim for 1000 mg Calcium daily. Use Calcium calculator https://www.iofbonehealth.org/calcium-calculator
Calcium supplementation alone should not be recommended as a means of fracture prevention in those not on a bisphosphonate.

If there is adequate Calcium and vitamin D intake then no supplementation is required. Elderly patients that are housebound or living in residential/ nursing homes are likely to gain benefit from lifelong calcium + vitamin D supplementation.

A combination treatment of calcium and vitamin D is recommended if both are required and to aid compliance. However, compliance and persistence with supplementation is poor.

**Formulary choices:**

<table>
<thead>
<tr>
<th>Brand and dose</th>
<th>Dose</th>
<th>Formulation</th>
<th>28 day cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accrete D3 tabs (calcium 600mg+VitD3 400units)</td>
<td>Take one twice daily</td>
<td>Film coated tablets</td>
<td>£2.75</td>
</tr>
<tr>
<td>Evacal D3 (calcium 600mg+VitD3 400units)</td>
<td>Take one twice daily</td>
<td>Chewable tablet</td>
<td>£2.75</td>
</tr>
<tr>
<td>Calfovit D3 sachet (calcium 1200mg+Vit.D3 800 units)</td>
<td>Take one daily</td>
<td>Sachet (useful if unable to swallow tablets or capsules)</td>
<td>£4.03</td>
</tr>
<tr>
<td>Adcal D3 CAPLET (calcium 300mg + VitD3 200units)</td>
<td>Take TWO twice daily</td>
<td>Caplet (smaller size if unable to swallow tablets/capsules; stability in a MCA for up to 14days)</td>
<td>£2.95</td>
</tr>
<tr>
<td>Calci-D (calcium 1000mg + VitD3 1000units)</td>
<td>Take one daily</td>
<td>Chewable tablet (as an option for patients with compliance issue)</td>
<td>£2.25</td>
</tr>
</tbody>
</table>

*Mims February 2019

Calcium supplements should not be taken within two hours of bisphosphonates. As the dose is supplemental, routine monitoring is not thought necessary except in patients with renal impairment where caution is advised. Avoid in patients with hypercalcaemia, metastatic calcification and a history of calcific renal stones.
The following treatments may be considered by specialist if first/second line treatments are not suitable or not tolerated

**Denosumab** JAPC traffic light status: AMBER
Denosumab 60mg (injected every 6 months) may be used under the shared care agreement. Compliance with NICE TA 204 criteria (listed below) from the specialist should be evidenced.

- Primary prevention of osteoporotic fragility fractures in patients who are intolerant, contraindicated, or unable to comply with special instructions for administering alendronate and risedronate and who have a combination of T-score, age and number of independent clinical risk factors for fractures as indicated in the following table.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>NOT recommended</td>
<td>−4.5</td>
<td>−4.0</td>
</tr>
<tr>
<td>70-74</td>
<td>−4.5</td>
<td>−4.0</td>
<td>−3.5</td>
</tr>
<tr>
<td>75 or older</td>
<td>−4.0</td>
<td>−4.0</td>
<td>−3.0</td>
</tr>
</tbody>
</table>

- Secondary prevention of osteoporotic fragility fractures in patients who are intolerant, contraindicated, or unable to comply with special instructions for administering alendronate and risedronate.

It is important to check calcium & vitamin D levels before each dose due to risk of severe hypocalcaemia (MHRA 2012). ONJ occurs rarely with denosumab (MHRA 2014) and good oral hygiene practices should be maintained during treatment.

Denosumab for the treatment of bone loss associated with hormone ablation in men with prostate cancer is RED in Derbyshire.

**Hormone Replacement Therapy**
HRT is recommended by the National Osteoporosis Society for women under the age of 60 years when the benefits of treatment outweigh the risks. There are a large number of formulations of oestrogen or oestrogen plus progestagen combinations, some of which are licensed. The unfavourable risk/benefit balance in older postmenopausal women, suggest that the use of HRT for osteoporosis prevention is mostly restricted to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms.

**Parathyroid hormone (teriparatide)** JAPC traffic light status: RED
This is licensed for the treatment of osteoporosis but should be reserved for specialist advice. It has been designated a RED drug in Derbyshire and will be under the care of secondary care. Duration of treatment is to 2 years.

**Selective oestrogen receptor modulator (Raloxifene)** GREEN after specialist initiation
Licensed for the treatment of post-menopausal osteoporosis but should be reserved after consultant initiation at a dose of 60mg per day taken at any time without regard to meals. Treatment is likely to be more effective if calcium and vitamin D is also given.

**Zoledronic acid** JAPC traffic light status: RED
Intravenous bisphosphonates are options for treating osteoporosis in adults who have been assessed as being at higher risk of osteoporotic fragility fracture as per NICE TA464. Choice of treatment is made on an individual basis after informed discussion with a specialist.

Zoledronate has been associated with renal impairment, therefore in patients at risk e.g. pre-existing renal disease, renal function monitoring should be considered.
6. Biochemical markers of bone turnover in osteoporosis
The place of biochemical indicies of skeletal turnover still requires further research before used in routine clinical practice. These include the use osteocalcin, N-terminal propeptide of type 1 procollagen (P1NP), N-telopeptide of type 1 collagen (NTX), C-terminal telopeptide of type 1 collagen (CTX), and pyridinoline cross-links.

Reference
1. Osteoporosis: assessing the risk of fragility fracture- NICE CG146. August 2012
2. SIGN 142: Management of osteoporosis and the prevention of fragility fractures. March 2015
3. JAPC-Guidance on the prevention, diagnosis and management of Vitamin D deficiency in primary care- May 2016
6. NICE TA464 Bisphosphonates for treating osteoporosis. August 2017 updated July 2019

Authors
Clinical Effectiveness Team in collaboration with Dr. Roger Stanworth, Michelle Hui, Antonia Ugur, Lit-Hiang Lee, Osteoporosis MDT Royal Derby Hospital, and Dr Paul Masters on behalf of CRHFT.

<table>
<thead>
<tr>
<th>Document Update</th>
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<tbody>
<tr>
<td>p.3 &amp; p.7 amended as per NICE TA464 update to remove reference to 1% &amp; 10% 10-year fracture probability. Appendix 1 PDA updated as per NICE.</td>
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<tr>
<td>Date</td>
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<tr>
<td>June 2020</td>
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</tbody>
</table>
Appendix 1: Effect of bisphosphonates on the risk of fractures
(see NICE patient decision aid- Bisphosphonates for treating osteoporosis)

**Effect of bisphosphonates on the risk of vertebral (spinal) fractures**

10 in 100 (10%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 90 people will not have a vertebral fracture and would not have done anyway
- about 5 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 5 people get vertebral fractures even though they have bisphosphonate treatment.

20 in 100 (20%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 80 people will not have a vertebral fracture and would not have done anyway
- about 11 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 9 people get vertebral fractures even though they have bisphosphonate treatment.

30 in 100 (30%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:

- about 70 people will not have a vertebral fracture and would not have done anyway
- about 16 people avoid getting vertebral fractures because they have bisphosphonate treatment
- about 14 people get vertebral fractures even though they have bisphosphonate treatment.

*It is not possible to know in advance what will happen to any individual person.*
Effect of bisphosphonates on the risk of hip fractures

5 in 100 (5%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:
- about 95 people will not have a hip fracture and would not have done anyway
- about 2 people avoid having a hip fracture because they have bisphosphonate treatment
- about 3 people have a hip fracture
- even though they have bisphosphonate treatment.

10 in 100 (10%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:
- about 90 people will not have a hip fracture and would not have done anyway
- about 3 people avoid having a hip fracture because they have bisphosphonate treatment
- about 7 people have a hip fracture
- even though they have bisphosphonate treatment.

20 in 100 (20%) baseline risk

On average, for every 100 people at this baseline risk who have bisphosphonate treatment for at least 3 years, over 10 years:
- about 80 people will not have a hip fracture and would not have done anyway
- about 7 people avoid having a hip fracture because they have bisphosphonate treatment
- about 13 people have a hip fracture
- even though they have bisphosphonate treatment.

It is not possible to know in advance what will happen to any individual person.