Nottinghamshire osteoporosis and fracture prevention guideline for Primary Care

This guideline is based on the recommendations from NICE, NOGG, SIGN, Dutch and Canadian national guidelines, and the local expert opinion.

NO PREVIOUS FRAGILITY FRACTURE / PRIMARY PREVENTION

Assess the risk factors and calculate FRAX* score for:
- any postmenopausal women,
- any men aged 50 and over,
- any patient with a clinical risk factor (see tables).

For all patients provide: lifestyle advice + Ca & vit D (self-care/diet) + assess h/o falls if over age of 65 or >50 and with condition that could increase the risk of falls & refer to Falls Team if indicated

LOW RISK OF FRACTURE	INTERMEDIATE RISK OF FRACTURE	HIGH RISK OF FRACTURE or BMD T≤ -2.5	VERY HIGH RISK OF FRACTURE or BMD T≤ -3.5

Clinical assessment + investigations

DXA to measure BMD

Recalculate FRAX with BMD

FRAX at/above intervention threshold
or
DXA not practical (i.e. frailty, >89yo)
or
BMD T -1.0 to -2.4 and age ≥65yo

NO / YES

Reassess risk factors and FRAX in 5 years or sooner if needed (i.e. following fragility fracture or change in risk factors).

INITIATE TREATMENT

1st line: ALENDRONIC ACID 70 mg once weekly (if CrCl ≥35mL/min)

2nd line: RISEDRONATE 35mg once weekly (if CrCl ≥30mL/min)

+

request DXA - baseline BMD for review and to confirm/guide treatment choice, to check for vertebral fractures, and to verify if referral needed. If DXA not practical - for clinical decision regarding treatment based on patient priorities.

Review tolerance and adherence at 3, 6 and 12 months. Continue treatment for at least 5 years. Then review fracture risk to aid decision on treatment break – see treatment review.

Refer to Specialist for parenteral treatment. If no contra indication, initiate oral bisphosphonate while awaiting Specialist review.

Refer to Specialist all patients with:
- BMD T≤ -3.5
- recent (within 2 years) or multiple vertebral fractures identified on DXA (VF Gr2 or ≥2 Gr3) or opportunistically,
- hip fracture,
- CrCL <30mL/min if bone treatment is indicated (refer to renal),
- requirement for other bone treatment (e.g., zoledronate, denosumab, or anabolics)
- fractures despite good compliance with oral treatment lasting >12 months.

WHEN CALCULATING FRAX REMEMBER:
- Use FRAX for the country of birth, even if lived in UK most of life (e.g., UK flag on right hand side of page for patients born in UK).
- If patients had >1 fall in the last year, increase MOF & hip fracture probability by 30% of the score.
- If patients have T2DM, enter 'yes' in the RA question.

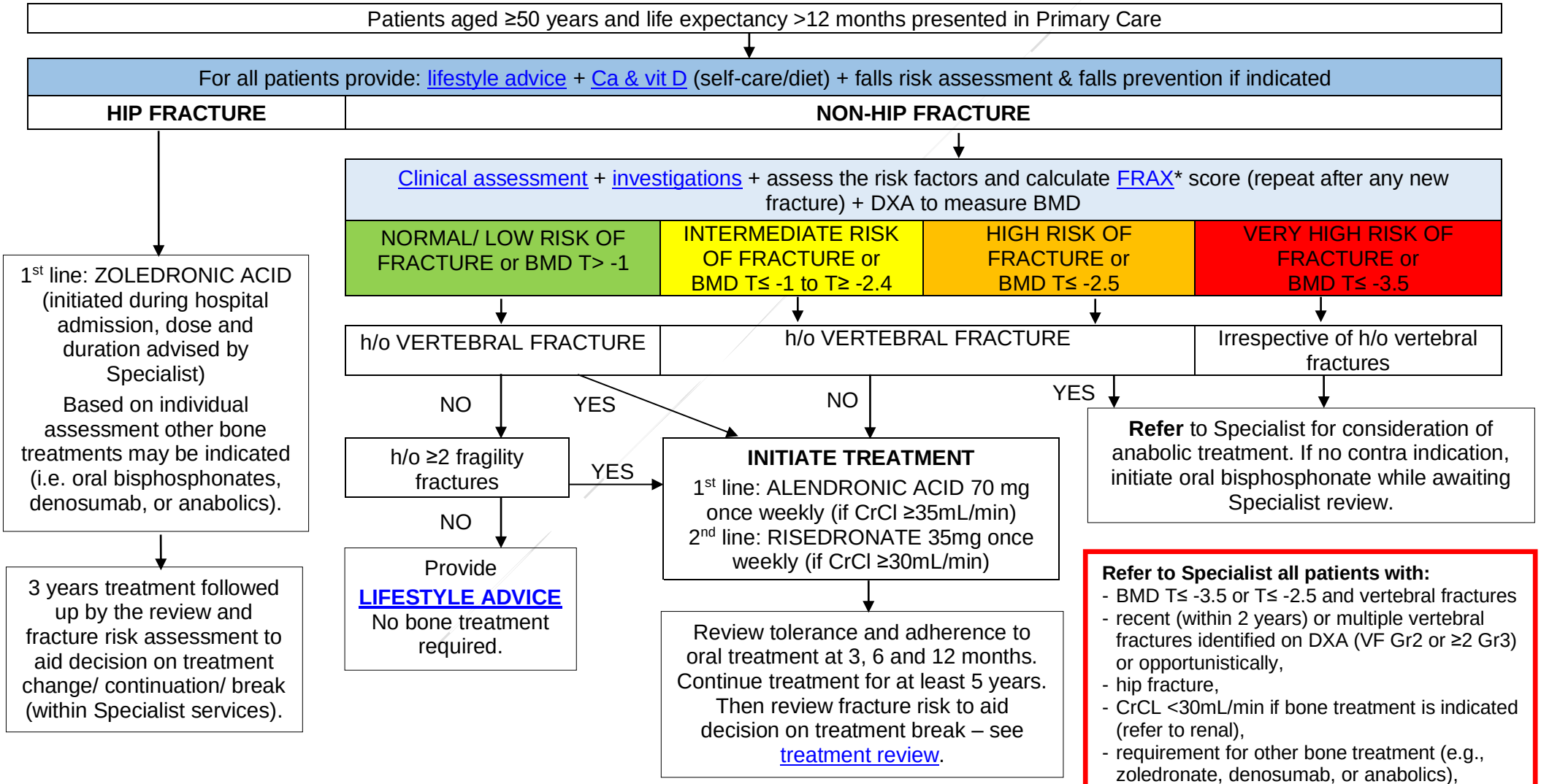
Notes on primary prevention:

- When assessing the risk of fracture using FRAX tool - **use the highest of the two FRAX scores**, to guide treatment decision.
- **Patients under the age of 40-years** who in the presence of multiple or significant risk factors require fracture risk assessment – should be assessed using BMD and not FRAX assessment tool.
- **All patients over the age of 90** are regarded as in high risk of fragility fracture. However, the decision to initiate bone protective treatment should be based on shared decision making and individual assessment considering life expectancy and risks vs benefits.

HISTORY OF FRAGILITY FRACTURE / SECONDARY PREVENTION

Post-fracture, all patients who are not under the ongoing care of Bone Health Specialist/Service, should be followed up in Primary Care at 4 and 12 months with aim to:

- review medication and risk factors which may increase the risk of falls/fracture (calculating FRAX score if not already done following recent fracture),
- ensure optimised intake of calcium and vitamin D, and
- monitor adherence to any bone treatment prescribed (and if no treatment, review if this is clinically appropriate).

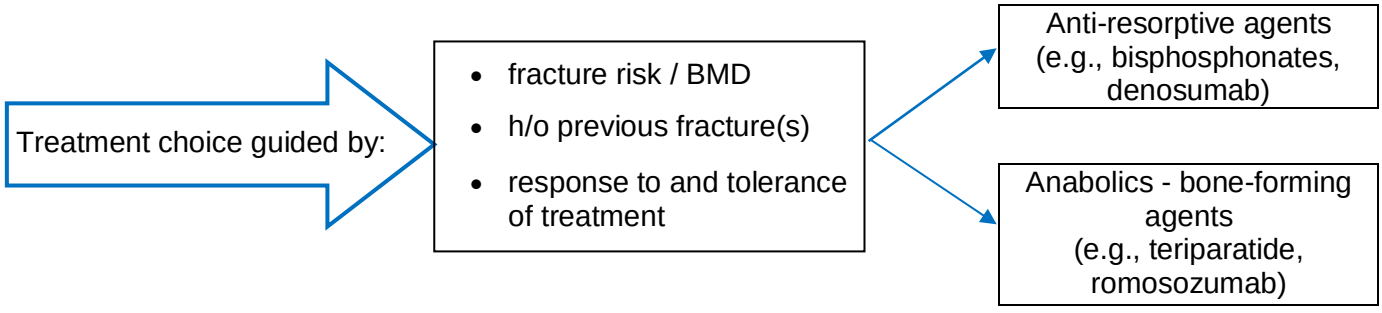


TREATMENT CHOICE SUMMARY

See appendix 1 for more information on individual treatments, dosing schedule and duration.

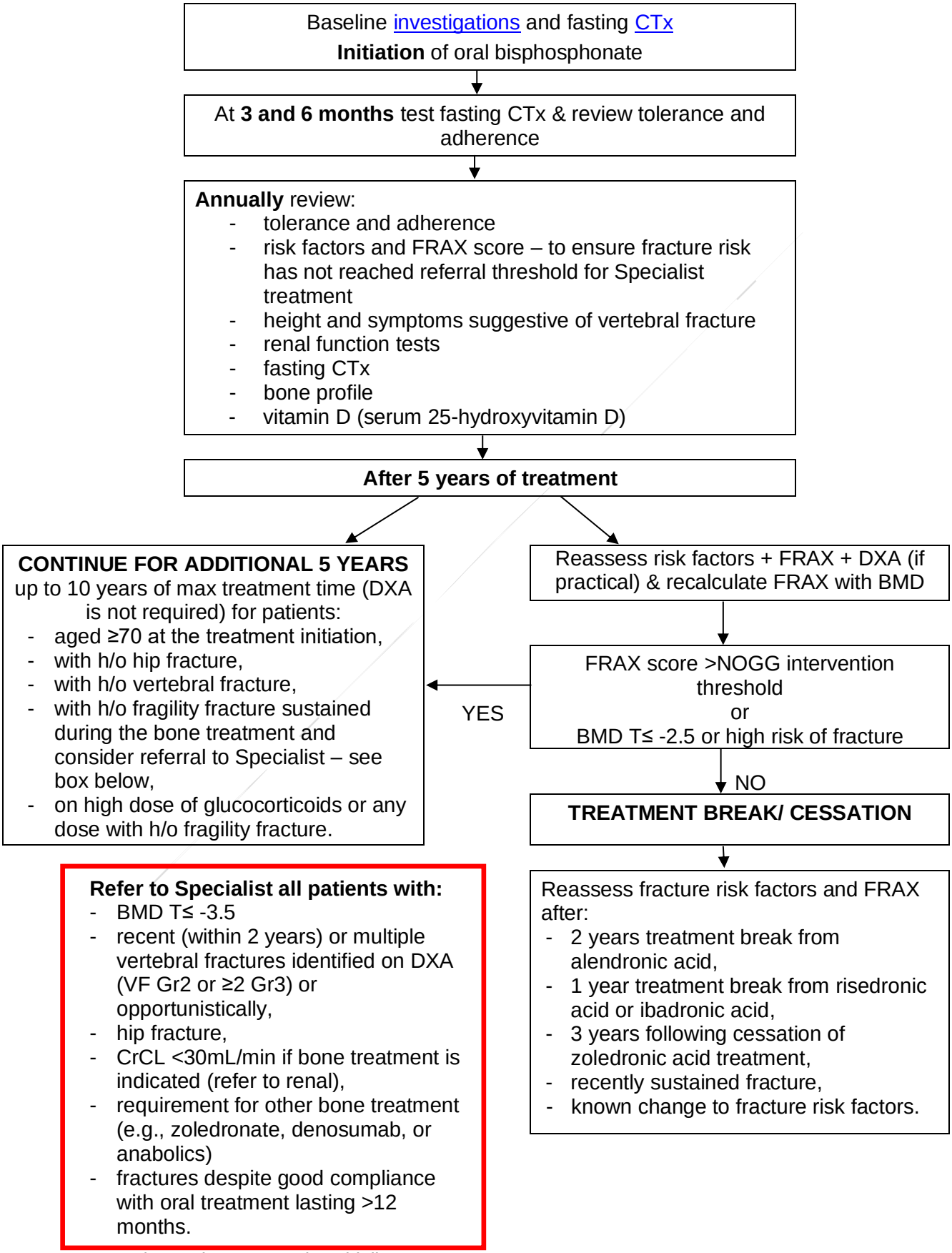
Where patient decision support is required on the initiation of bone-sparing treatment for osteoporosis see NICE bisphosphonates for treating osteoporosis patient decision aid.

INDICATION	TREATMENT
Patients with osteoporosis and no previous fracture or for primary prevention	Bisphosphonates are the most cost-effective drug treatment option: 1st line - alendronic acid 70mg once a week 2nd line - risedronate 35mg once a week If oral bisphosphonates are not appropriate due to clinical contra-indications, adverse reactions & side effects, or inability to follow administration & dosing directions use 3rd line - intravenous zoledronic acid 5mg* once a year. Requires referral to FLS/Secondary Care for Specialist initiation. *Based on the national consensus, local Specialists support the use of 4mg dose for this indication.
All patients at very high risk of fractures	Initiate oral bisphosphonate and refer to specialist to consider anabolic treatment (teriparatide or romosozumab): 1st line - alendronic acid 70mg once a week 2nd line - risedronate 35mg once a week
Following hip fracture	1st line – intravenous zoledronic acid 5mg* once a year (reduces mortality and recurrence of fracture). Requires referral to FLS/Secondary Care for Specialist initiation. *Based on the national consensus, local Specialists support the use of 4mg dose for this indication.
Following vertebral fracture in patients with intermediate risk of fracture or BMD< -1	Initiate oral bisphosphonate and refer to specialist to consider anabolic treatment (teriparatide or romosozumab): 1st line - alendronic acid 70mg once a week 2nd line - risedronate 35mg once a week
For secondary prevention following any other fractures	1st line - alendronic acid 70mg once a week 2nd line - risedronate 35mg once a week And refer to a Specialist if meets criteria – see page 4.
Only for women with menopausal symptoms and at high risk for fracture	HRT – see NICE NG23 guideline: Menopause: diagnosis and management.
Only for postmenopausal women and only for secondary prevention, where other treatments are unsuitable or contra-indicated (not suitable for men)	Raloxifene 60mg to be taken orally once a day – locally classed Amber 2 (on Specialist recommendation).



MONITORING AND TREATMENT REVIEW

- All parenteral bone treatments should be regularly reviewed within Specialist services alongside the treatment administration during ongoing therapy.
- For patients who completed zoledronic acid therapy and have been discharged from Specialist care, the fracture risk assessment should be undertaken within Primary Care after 3 years.



BONE TURNOVER MARKERS

Bone turnover markers (BTM) can be a useful tool in measuring efficacy of antiresorptive medication, particularly where compliance is unclear, and to determine duration of bisphosphonate treatment suspension.
The most commonly used BTM are:

- CTx - a bone resorption marker (serum C-terminal telopeptide of type I collagen) - the preferred test in Nottinghamshire,
- PINP - a bone formation marker (serum propeptide of type I collagen) – may be preferred in other areas (i.e. Bassetlaw and South Yorkshire).

All BTM are elevated after recent fracture and therefore levels are difficult to interpret in the immediate post fracture period (pragmatically, up to a year).

CTx:

- requires a fasting sample as results are affected by food intake (only water pre-test),
- purple top tube - samples should be collected in EDTA to ensure stability for up to 24 hours (other sample tubes are not advised for stability reasons),
- a 30% reduction from baseline of CTx is considered to indicate a significant reduction in bone turnover.

REPEAT DXA SCAN

DXA scans should only be undertaken if the result will change management. For most individuals, there is little reason to repeat DXA until at least five years after starting treatment.

DXA scans are sometimes repeated after a course of osteoporosis treatment (for detailed rationale please see NOGG guidance for more information). However, treatments are designed to reduce risk of further fracture, and the reduction in fracture risk with appropriate treatments for osteoporosis (typically, 50-60% for vertebral fracture and 30% for non-vertebral fractures) is much greater than BMD change (typically 1-2% per annum with bisphosphonates, mainly due to excess mineralisation in bone with reduced turnover).

SUPPORTING INFORMATION

1. ASSESMENT OF RISK FACTORS FOR FRAGILITY FRACTURE

Aims to identify risk factors and to assess for signs of undiagnosed vertebral fracture in the following groups:

- any postmenopausal women,
- any men aged 50 and over,
- any patient over the age of 50 with a clinical risk factor - see tables below.

Key notes:

- Use holistic clinical review and Fracture Risk Assessment Tool (FRAX®) to assess the risk of fragility fracture and to help clinical decision on initiation of bone sparing treatment in patients aged 50-90 years old.
- FRAX tool may not include or assess all the present risk factors which need to be considered when assessing the risk of fracture for a patient.
- In patients under the age of 40 who present with a major risk factor for fragility fracture, use DXA to measure BMD and to assess the risk of fracture (do not use FRAX).
- Patients at low risk of fragility fracture should be routinely re-assessed every 5 years or following fracture or change in the clinical risk factors.
- The major risk factors should prompt fracture risk assessment in all patients of any age.

MAJOR RISK FACTORS FOR FRAGILITY FRACTURE AND OSTEOPOROSIS
- previous fragility fracture (low-trauma fracture e.g. fall from a standing height or less) - history of early untreated menopause (below age of 45) - oral/systemic glucocorticoids (for ≥3 months at a dose equivalent to ≥7.5mg of prednisolone daily)

OTHER RISK FACTORS FOR FRAGILITY FRACTURE AND OSTEOPOROSIS
PATIENT & LIFESTYLE: - parental history of hip fracture - height loss (>4cm) - thoracic kyphosis - low BMI (<20kg/m^2) - current smoking (risks associated with vaping unknown) - alcohol intake >3 units per day - any fall - frailty (CFS 5 or more) - low BMD of femoral neck (if known)
CO-EXISTING DISEASES: - rheumatoid arthritis and other inflammatory diseases - diabetes type1 and type 2 - hypogonadism and other endocrine disease (e.g. hyperparathyroidism, hyperthyroidism, Cushing's disease/syndrome) - thyroid cancer with suppressed TSH - haematological disorders (e.g. multiple myeloma, thalassaemia**)** - Malabsorption or malnutrition (e.g. post bariatric surgery, coeliac disease, inflammatory bowel disease) - calcium or vitamin D deficiency - institutionalized patients - chronic respiratory conditions - chronic liver disease - moderate to severe chronic kidney disease (CKD 3a-5) - human immunodeficiency virus - neurological or psychiatric diseases (e.g.. Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, depression) - Muscular conditions (e.g. myositis, myopathies and dystrophies, sarcopenia**)**
CO-PRESCRIBED MEDICATIONS (not an exhaustive list): - drugs affecting gonadal hormone production (aromatase inhibitors, androgen deprivation therapy, medroxyprogesterone acetate, gonadotrophin hormone releasing agonists, gonadotrophin hormone receptor antagonists) - anti-epileptics - proton pump inhibitors – when used long term (>1year), see MHRA Drug Safety Update - some immunosuppressants (calmodulin/calcineurine phosphatase inhibitors) - long-term antipsychotics - pioglitazone

2. DIAGNOSING OSTEOPOROSIS

Diagnosis of osteoporosis is based on multiple factors, particularly, a history of low trauma fracture. Osteoporosis is a significant risk factor for future fragility fracture.

CLINICAL ASSESSMENT of individuals presenting with fragility fractures/osteoporosis should:
• exclude non-osteoporotic causes of fragility fracture (i.e., metastatic bone cancer, multiple myeloma, osteomalacia, Paget's disease), • identify any potential secondary cause(s) of osteoporosis (i.e., endocrine disorders, malabsorption, metabolic bone disorders), • include assessment for symptoms of undiagnosed vertebral fractures (i.e., height loss, back pain, kyphosis), • optimise regular medications and include management of co-morbidities, • include lifestyle advice: smoking cessation, safe alcohol consumption, weightbearing activity, and dietary vitamin D and calcium intake, • falls risk assessment, • frailty assessment, • Fracture Risk Assessment Tool (FRAX®) may be used **to support the diagnosis** of osteoporosis and for identifying patients for primary prevention.

CLINICAL INVESTIGATIONS should include:
• renal function tests - refer to renal team if CrCl <30ml/min, if not already known to them • liver function tests • thyroid function tests • parathyroid hormone test • full blood count • C-reactive protein • bone profile (including serum corrected calcium) • vitamin D (serum 25-hydroxyvitamin D) • fasting CTx (as a baseline if likely to initiate oral bisphosphonate) • referral for X-ray of the fracture or lateral X-rays of the lumbar and thoracic spine when there is spinal pain, loss of height, or kyphosis.

INTERPRETATION OF BONE DENSITY (BMD) SCANS:

Dual Energy X-ray Absorptiometry (DXA) scanning may help to establish the diagnosis or **to guide treatment decision.** But it is not a requirement for making a diagnosis or initiation of bone sparing treatment. For example, osteoporosis can be confidently diagnosed and treated **without** DXA in the following situations:

- postmenopausal women >64 years old with vertebral compression fractures (VCFs) in the absence of a pertinent history of trauma,
- a neck of femur (NOF) fracture in patients > 74 year old,
- a fragility fracture in patients with moderate to severe frailty (CFS >6) or in people >90 years old.

The use of BMD alone to assess fracture risk has a high specificity but low sensitivity. Thus, although individuals with lower BMD are at highest individual risk for osteoporotic fractures, **most osteoporotic fractures will occur in people who do not have T-score lower than -2.5.**

BMD results should not be reviewed in isolation when making the diagnosis of osteoporosis in an individual with a low-trauma fracture; it is important to also consider the individual patient factors and characteristics which are present.

DXA scans give results in absolute terms (g/cm2), noting that this is an areal measurement of a volume and in relative terms:

- T-score (a measure of bone density compared with the mean and standard deviations (SD) for young healthy adults of the same sex),
- Z-score (compared with age- and gender-matched population).

T-score range	BMD description	Additional information
-1 to +2	"normal" bone	
-1 to -2.4	osteopenia	This is not a disease state, but a description of Bone Mineral Density (BMD) relative to young healthy individuals. To illustrate, by definition, 1 in 6 people will have BMD more than one SD below average at the age of 20-30 years, so will have an "osteopenic" T score. The clinical utility of identifying osteopenia depends on the individual patient (e.g., it may provide the rationale for considering bone protection in someone on high-dose steroids); but it does not necessarily require management or monitoring.
-2.5 and below	osteoporosis	Loss of bone tissue and structural changes, leading to a loss of bone strength and an increased risk of low-trauma or 'fragility' fractures (occurs after a fall from standing height or less, may happen following even minor stress such as a trip, bending over, coughing, or lifting; most commonly affecting spine, hips, and wrist).

THE GRADES OF VERTEBRAL FRACTURES (VF) REPORTED ON DXA:

The scale looks at the shape of the vertebrae and measures the loss of height (LOH). It starts at:

- grade 0 for normal vertebrae,
- grade 1 (VF Gr1) for mild fracture of 20 to 25% LOH,
- grade 2 (VF Gr2) for moderate fracture 25 to 40% LOH,
- grade 3 (VF Gr3) for severe fracture showing LOH at greater than 40%.

3. AROMATASE INHIBITOR THERAPY OR ANDROGEN-DEPRIVATION THERAPY AND PREVENTION OF OSTEOPOROSIS

- Therapy with aromatase inhibitors for breast cancer and androgen deprivation therapy for men with prostate cancer is recognised secondary cause of osteoporosis.
- All patients starting those treatments should have fracture risk assessment using FRAX and, where practical, DXA to measure BMD.
- The relevant local guideline for using bisphosphonates in breast cancer patients on aromatase inhibitors can be found here: Nottingham Breast Institute Guidance.

4. PEOPLE WITH EATING DISORDERS - see NICE NG69 guideline for information on management of low bone mineral density.

5. GLUCOCORTICOID-INDUCED OSTEOPOROSIS AND PREVENTION

Initiation of bone-protective therapy is recommended, at the same time as initiation of oral or systemic glucocorticoid (without FRAX/waiting for a DXA result) in the following people:
• anyone with a prior fragility fracture prescribed steroids at any dose (if not already on bone-sparing treatment), • women and men aged ≥70 years prescribed oral steroids at any dose, • anyone commencing high dose corticosteroids **(≥7.5mg per day prednisolone or its equivalent for ≥3 months, or ≥30mg per day for >30 day, or cumulative doses ≥5g per year**).

For all other adults aged >40 years, undertake fracture risk assessment when initiating oral or systemic glucocorticoid with ≥2.5mg per day prednisolone or its equivalent for >3 months.

Key notes:

- The highest rate of bone loss occurs within the first 3-6 months of starting oral or systemic steroid therapy and decreases rapidly after cessation of treatment.
- Use FRAX only for patients aged >40 years. For patients aged 30-40 years, use DXA to measure BMD. People aged <30 would not yet have reached peak bone mass, hence DXA may not be appropriate.
- Patients initiated on less than prednisolone 7.5mg/ day (or equivalent) who have a FRAX probability near to, but below, the intervention threshold should have their FRAX repeated after 12-18 months with DXA and BMD if they remain on steroids.
- 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.
- For adults, who do not require bone protective therapy at the initiation of low dose/short course of steroid treatment the lifestyle advice should be provided, including optimising dietary intake and self-care supplementation of calcium and vitamin D – see below.
- The long term risk of bone loss associated with use of topical and inhaled glucocorticoids, even at high doses, is extremely small when compared to oral and systemic treatments. Currently the evidence on bone loss secondary to long term use of high dose inhaled glucocorticoids is inconclusive and may suggest some susceptible individuals may be affected.

TREATMENT OPTIONS FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS:

Alendronic acid 70mg once weekly/ risedronate 35mg once weekly (off-label indication) - For those expected to be on long-term steroids (more than 3 months), plan for a treatment duration of 5 years then review. - For those expected to be on short-term steroids (less than 3 months), consideration should be given for use of a shorter-acting bisphosphonate (e.g., risedronate), particularly in younger individuals. This should be for the duration of the steroid treatment.
Zoledronic acid - For those on long term steroids, plan for a treatment duration of 6 years or longer.

On discontinuation of glucocorticoid treatment, if there is no other indication to continue bone-sparing therapy, re-assess fracture risk using FRAX score. If both fracture risk scores are below the intervention threshold, bone-sparing therapy may be stopped.

For further guidance on the prevention of glucocorticoid induced osteoporosis and for advice on management beyond the scope of this guideline please refer to: Glucocorticoid Induced Osteoporosis Clinical Practice Guidelines by American College of Rheumatology (updated 09/07/2022) https://rheumatology.org/glucocorticoid-induced-osteoporosis-guideline#2022-giop-guideline

6. LIFESTYLE ADVICE

The following advice should be provided to all patients as part of bone health management:

- a combination of regular weight-bearing and muscle strengthening exercise for 20 minutes three times a week, tailored according to the individual patient's need and ability – see Exercise for bones.
- adequate calcium and vitamin D intake – see below. Also, provide advice on recommended sun exposure to maximise vitamin D levels – patient information leaflet.
- a healthy, nutrient-rich balanced diet and normal body weight (where possible) should be maintained. See Further food facts and bones | Royal Osteoporosis Society (strwebprdmedia.blob.core.windows.net) for dietary advice and osteoporosis.
- avoidance of excessive alcohol consumption - advise men and women to restrict alcohol consumption to < 2 units per day,
- smokers should be advised to stop smoking and offered referral to smoking cessation services,
- in all patients over the age of 65 or those at risk of falling perform falls risk assessment (see NICE guidelines 2013).

7. CALCIUM AND VITAMIN D

- The **minimum calcium intake recommended for adults is 700mg daily, or 1000mg (1g) daily if on antiresorptive treatment.** See Calcium Calculator. Preferably achieved through dietary intake, or if not possible, by oral supplementation.
- If calcium supplementation is indicated for patients on oral bisphosphonates, it should be taken at least 2 hours apart (reduced effectiveness). There is little additional benefit of calcium supplementation in individuals with excellent dairy intake (3-4 serves a day, equivalent to >1g daily), whether or not they are on antiresorptive treatment. See Osteoporosis: Calcium for more information on calcium and osteoporosis.
- The **minimum recommended vitamin D intake for adults is at least 400 IU daily, or 1000 IU daily if on antiresorptive treatment.** In those patients NHS prescribing of vitamin D maintenance dose is clinically appropriate. See local vitamin D guideline.
- In individuals on antiresorptive treatment, the minimum recommended serum 25(OH)D level is >50nmol/L (within the "sufficient levels") and >70nmol/L before going into winter. In this cohort vitamin D annual testing may be clinically appropriate, as part of the bone disease management.
- For patients about to start a parenteral anti-resorptive agent (e.g., zoledronic acid or denosumab), rapid correction of vitamin D deficiency may be required (to reduce the risk of hypocalcaemia). If serum 25(OH)D level is below 50nmol/L, prescribe the treatment loading regimen followed by regular maintenance doses. See local vitamin D guideline.
- Housebound, residential, nursing home or elderly patients, are more likely to require calcium and vitamin D supplementation to achieve recommended levels of intake.

8. PATIENT INFORMATION RESOURCES

- Information for patients diagnosed with osteoporosis from Royal Osteoporosis Society: about-osteoporosis-and-weaker-bones-easy-print-version.pdf (strwebprdmedia.blob.core.windows.net)
- Information for patients on the prevention and treatment of osteoporosis in the NOGG Clinical Guideline: NOGG-PIL-2021-f.pdf
- Information for patients on calcium intake (includes calcium calculator) from Royal Osteoporosis Society: Osteoporosis: Calcium (theros.org.uk)
- Information for patients on vitamin D and bone health from Royal Osteoporosis Society: Osteoporosis: Vitamin D for bones (theros.org.uk)
- Information for patients on healthy diet and bone health from Royal Osteoporosis Society: Further food facts and bones | Royal Osteoporosis Society (strwebprdmedia.blob.core.windows.net)

- Information for patients on recommended exercise for bone health: Exercise for bones
- Osteoporosis risk checker for general public who have not been diagnosed with low bone density mass: Osteoporosis risk checker (theros.org.uk)
- Bisphosphonates for treating osteoporosis Patient decision aid from NICE: TA464 Patient decision aid on bisphosphonates for treating osteoporosis (nice.org.uk)

9. REFERENCES AND FURTHER RESOURCES FOR CLINICIANS

- NICE clinical guideline [CG146]. Osteoporosis: assessing the risk of fragility fracture. National Institute for Health and Care Excellence. Available here: https://www.nice.org.uk/guidance/cg146/
- Clinical guideline for the prevention and treatment of osteoporosis 2021, National Osteoporosis Guideline Group UK (NOGG). Available here: https://www.nogg.org.uk/full-guideline
- Management of osteoporosis and the prevention of fragility fractures, SIGN national clinical guidance 142, revised January 2021. Scottish Intercollegiate Gidelines Network. Available here: https://www.sign.ac.uk/media/1812/sign-142-osteoporosis-v3.pdf
- Fracture Risk Assessment Tool (FRAX®). Centre for Metabolic Bone Diseases, University of Sheffield. Available here: frax.shef.ac.uk/FRAX/tool.aspx?country=9
- Glucocorticoid-induced osteoporosis guideline 2022. American College of Rheumatology. Available here: 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis - Humphrey - 2023 - Arthritis & Rheumatology - Wiley Online Library
- Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment 2002. Bone and Tooth Society of Great Britain, National Osteoporosis Society, Royal College of Physicians. Available here: https://cdn.shopify.com/s/files/1/0924/4392/files/glucocorticoid-induced-osteoporosis-guideline.pdf
- Call to action: a five nations consensus on the use of intravenous zoledronate after hip fracture. Johansen A, Sahota O, Dockery F, Black AJ, MacLullich AMJ, Javaid MK, Ahern E, Gregson CL. Age Ageing. 2023 Sep 1;52(9):afad172. doi: 10.1093/ageing/afad172. Erratum in: Age Ageing. 2024 Jan 2;53(1):afae014. doi: 10.1093/ageing/afae014. PMID: 37776543; PMCID: PMC10542103. Available here: https://pubmed.ncbi.nlm.nih.gov/37776543/
- Guidelines for the adjuvant use of endocrine treatments and bisphosphonates for early breast cancer. Nottingham University Hospitals NHS Trust. Available here: https://nuhp.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=e16f1cc0851827622a628e751d9d2d01

Appendix 1

DRUG INFORMATION

For full list of side effects, cautions and contraindications, please see the BNF and Summary of Product Characteristics. Some of these drugs are subject to MHRA alerts, please follow provided links for further details.

ORAL BISPHOSPHONATES Green	
DOSE:	Alendronic acid – 70mg once weekly (off-label in men) (CrCl ≥ 35ml/min) – 1st line Risedronate sodium – 35mg once weekly (CrCl ≥ 30ml/min) – 2nd line Weekly dosing off-label for the management of glucocorticoid-induced osteoporosis.
Recommended duration of therapy	Check treatment tolerance and adherence after 3 and 6 months. Afterwards, re-check every 1 year. Continue treatment for 5 years. At 5 years, or sooner if fracture sustained or risk factors change, reassess adherence, risk factors and treatment choice. This may include a FRAX assessment and BMD measurement – see Review and monitoring of bisphosphonates. Longer durations of treatment, for up to 10 years, are recommended in the following men and women: • Age ≥70 years at the time that the bisphosphonate is started, or • Who have a previous history of a hip or vertebral fracture(s), or • Treated with oral glucocorticoids ≥7.5 mg prednisolone/day or equivalent, or • Who experience one or more fragility fractures during the first 5 years of treatment (if treatment is not changed). • After 10 years, treatment decisions should be made on an individual basis. Specialist advice may need to be sought.
Supporting information	NICE TA 464 bisphosphonates for treating osteoporosis patient decision aid MHRA/CHM advice - Bisphosphonates: atypical femoral fractures (June 2011) - Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis; atypical femoral fractures are considered a class effect of bisphosphonates. - During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain. - If suspected, immediately stop oral bisphosphonate and evaluate for incomplete femur fracture. MHRA/CHM advice - Bisphosphonates: osteonecrosis of the jaw (November 2009) - The risk of developing osteonecrosis of the jaw (ONJ) in association with oral bisphosphonates seems to be low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease. - There is clear evidence to suggest there is bisphosphonate-specific and indication-specific risk factors for ONJ such as potency (highest for zoledronic acid); route of administration (e.g., intravenous ibandronate, pamidronate, and zoledronic acid); and cumulative dose. - A history of dental disease, including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures is associated with an increased risk. - All patients with cancer should have a dental check-up before bisphosphonate treatment. All other patients who start bisphosphonates should have a dental examination only if they have poor dental status.

	- During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling of ONJ. - If suspected, immediately stop oral bisphosphonate and evaluate for osteonecrosis of the jaw. MHRA/CHM advice - Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal (December 2015) - The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma. - Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. - Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment.

ZOLEDRONIC ACID Red	
DOSE:	Licensed dosing: 5mg given intravenously every 12 months. Please make a note on GP system of the date of last administration to prevent inappropriate use of oral bisphosphonates. Based on the national consensus, local Specialists support the use of 4mg dose for osteoporosis and post-hip fracture. This is an off-label indication (4mg dose is licensed for prevention in patients with bone malignancies and treatment of tumor-induced hypercalcemia). Extended dosing interval (off-label): On specialist advice, the dosing interval may be extended up to 18 months in the non-hip fragility fracture population i.e., 3-4 doses administered over up to 4.5-6 years. As per SIGN guidance, the following patients may be suitable for extended interval dosing: Primary prevention: 1. age ≥ 65 years, 2. 10-year risk ≥10%, 3. DXA scan: T score -1.0 to -2.5 (if clinically appropriate or available). Secondary prevention: 1. age ≥ 65 years, 2. DXA scan: T score -1.0 to -2.5 (if clinically appropriate or available). It is increasingly clear that a lower dose and longer spacing between zoledronic acid treatments can still provide excellent fracture protection for women with osteopenia and men and women with osteoporosis. There is extremely similar reduction in fracture and improvement in BMD whilst acknowledging there is no head-to-head comparisons. All treatment decisions are individualised, patient centred and based on previous treatment success e.g., BMD, frailty, dementia, residential care considerations, contemporaneous glucocorticoid use, etc. Using bone turnover markers to guide dosing frequency may be a reasonable means of tailoring personalised approaches in individual patients, at clinician's discretion.
Recommended duration of therapy	3 years (or 3 doses for patients on extended dosing intervals) and then re-assess fracture risk. For patients on 12 monthly dosing schedules, longer durations of treatment, for at least 6 years, are recommended in the following men and women: • age ≥70 years at the time that the bisphosphonate is started,

	• who have a previous history of a hip or vertebral fracture(s), • treated with oral glucocorticoids ≥7.5 mg prednisolone/day or equivalent, • who experience one or more fragility fractures during the first 3 doses of treatment (if treatment has not changed).
Supporting information	**Post hip fracture** – 1st line treatment choice locally. In line with licensing, it is recommended to wait at least two weeks after hip fracture repair, although it is acknowledged that due to reasons of practicalities, it may be given earlier as patients must be provided infusion prior to discharge. MHRA/CHM advice - Denosumab (Xgeva®, Prolia®); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk (July 2015) The risk of osteonecrosis of the jaw should be explained to patients and the precautions to take, patients should be advised to: - tell their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures, they should make sure their dentures fit properly before starting treatment, - maintain good oral hygiene and get routine dental check-ups during treatment, - tell their doctor and dentist that they are receiving denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery, - tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge).

DENOZUMAB (Prolia®) Red	
DOSE:	60mg subcutaneous injection every 6 months
Recommended duration of therapy	Current evidence shows safety and efficacy are maintained for at least 10 years of treatment.
Supporting information	There is increased risk of multiple vertebral fractures within 18 months of discontinuation or when ongoing therapy is delayed. Denosumab should not be stopped without review and planned discontinuation by the Specialist. Treatment should be stepped down to alternative agent (e.g. bisphosphonate with satisfactory renal function). Recognised risk of hypocalcaemia: • denosumab is contraindicated in patients with hypocalcaemia; correct hypocalcaemia and vitamin D deficiency before starting treatment, • prior to each dose re-check serum calcium, vitamin D level, and renal function tests, • risk of post dose hypocalcaemia increases in patients with a CrCl of less than or equal to 30ml/min; check serum corrected calcium level two weeks after the first dose and advise to report any symptoms suggestive of hypocalcaemia e.g. muscle cramps, tingling, confusion, • patients established on haemodialysis or peritoneal dialysis - consider increasing monitoring frequency e.g., weekly levels for 4 weeks, • adequate intake of calcium and vitamin D is important in all patients.

	NICE TA204 - Denosumab for the prevention of osteoporotic fractures in postmenopausal women MHRA Drug Safety Update: Risk of vertebral fractures on interruption or cessation of treatment (2022): - Denosumab cessation leads to rapid reductions in BMD and elevations in bone turnover to levels above those seen before treatment initiation. Therefore, patients who discontinue denosumab have an increased risk of sustaining multiple vertebral fractures. - If denosumab therapy is stopped, prescribe an alternative treatment to prevent rapid bone loss e.g. zoledronic acid after the last injection of denosumab, if suitable. - If zoledronic acid is given post denosumab, bone turnover markers may be measured 3 and 6 months after administration of zoledronic acid. This can help to guide subsequent zoledronic acid infusions. MHRA/CHM advice - Denosumab (Xgeva®, Prolia®); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk (July 2015) – see more info in the table above

ABALOPARATIDE (Eladynos®) Red	
DOSE:	80 micrograms subcutaneous injection once daily for maximum duration of treatment 18 months
Recommended duration of therapy	Maximum 18 months
Supporting information	NICE TA991 - Abaloparatide for treating osteoporosis after menopause for post-menopausal women at very high risk of fracture. Stopping treatment - initiate anti-resorptive without delay after completion of the course. This should be planned at the initiation of abaloparatide to avoid a gap in treatment. Homecare - may be provided by a homecare service, which includes delivery of the injections and injection training, if required.

ROMOSOZUMAB (Evenity®) Red	
DOSE:	210mg subcutaneous injection once a month for 12 months
Recommended duration of therapy	12 months
Supporting information	To be prescribed in accordance with NICE TA 791 - Romosozumab for treating severe osteoporosis for post-menopausal women at high risk of fracture only if they have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within the last 24 months. Cardiovascular risk - contraindicated in patients with a history of myocardial infarction or stroke. Carefully consider cardiovascular risk vs fracture risk over the following 12 months and ensure shared decision making with patient. Hypocalcaemia - contraindicated in patients with hypocalcaemia; correct before starting treatment.

	Stopping treatment - initiate anti-resorptive without delay after completion of the course. This should be planned at the initiation of romosozumab to avoid a gap in treatment. Homecare - may be provided by a homecare service, which includes delivery of the injections and injection training, if required.

TERIPARATIDE (Forsteo®, Movymia®) Red	
DOSE:	20 microgram subcutaneous injection every day for 24 months
Recommended duration of therapy	24 months
Supporting information	To be prescribed in accordance with NICE TA 161 - Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women and NHS England » Interim Clinical Commissioning Policy Statement: Teriparatide for Osteoporosis in Men (Adults) Transient elevations in calcium - in normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of teriparatide. Therefore, if blood samples for serum calcium measurements are taken, this should be done at least 16 hours after the most recent teriparatide injection. Stopping treatment - initiate treatment with anti-resorptive without delay after completion of the course. This should be planned at the time teriparatide is instigated to avoid a gap in treatment. Homecare - is provided by a homecare service, which includes delivery of the injections and injection training if required. Patients should be deemed competent to self-administer or a suitable carer that can support a daily injection to facilitate treatment.

ALTERNATIVE TREATMENT OPTIONS	
Hormone Replacement Therapy (HRT) Green	Reduces the risk of fragility fracture in post-menopausal women (effects maintained for the duration of HRT therapy and decrease once HRT stopped). ee NICE guideline NG23 – Menopause diagnosis and management for further information.
Ibandronic acid oral Amb2	150mg tablet once a month (3rd line of oral bisphosphonate) No data available for hip fracture reduction. Not recommended if Creatinine Clearance ≤30ml/min.
Raloxifene Amb2	60mg tablet once a day Can be prescribed to post-menopausal women in accordance with NICE TA 160 (primary prevention) and NICE TA 161 (secondary prevention). Contraindicated in women with child-bearing potential, a history of venous thromboembolism, unexplained uterine bleeding, hepatic impairment, and severe renal impairment. Increased risk of VTE. Caution in women with a history of stroke or with risk factors for stroke.
Ibandronic acid injection (Bonviva®) Red	3mg IV injection every 3 months Only for post-menopausal women at increased risk of fracture, who do not tolerate oral bisphosphonates in line with NICE TA 464. However, IV ibandronate is not the usual first choice for parenteral bisphosphonates

	as although, a reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

FRACTURE PREVENTION EFFICACY OF DRUG TREATMENTS FOR POSTMENOPAUSAL WOMEN AND MEN WITH OSTEOPOROSIS WHEN GIVEN WITH CALCIUM AND VITAMIN D (from NOGG)

Intervention	Vertebral fracture	Non-Vertebral fracture	Hip fracture	Evidence of superiority or inferiority for vertebral fracture prevention in postmenopausal women with very high fracture risk	Licenced for use in Men
Romosozumab	Ib	IIb	IIb	Superior to Alendronate (Ib)	No
Teriparatide	Ia	Ia	Ia	Superior to Risedronate (Ib)	Yes
Alendronate	Ia	Ia	Ia	Inferior to Romosozumab (Ib)	Yes
Ibandronate	Ib	Ib	NAE	NAE	No
Risedronate	Ia	Ia	Ia	Inferior to Teriparatide (Ib)	Yes
Zoledronate	Ia	Ia	Ia	NAE	Yes
Calcitriol	IIa	NAE	NAE	NAE	Yes
Denosumab	Ia	Ia	Ia	NAE	Yes
HRT	Ia	Ia	Ia	NAE	No
Raloxifene	Ia	NAE	NAE	NAE	No
Strontium Ranelate	Ia	Ia	IIb	NAE	Yes

HRT: hormone replacement therapy
NAE: No available evidence
Ia: Systematic reviews or meta-analysis of level I studies with a high degree of homogeneity
Ib: Systematic reviews or meta-analysis with moderate or poor homogeneity
IIa: Systematic reviews or meta-analysis of level II studies
IIb: Level II studies (inappropriate population or lacking an internal control)

APPENDIX 2. COUNSELLING FOR PATIENTS ON BISPHOSPHONATES

All patients must be informed of the following information before starting on a bisphosphonate.

General advice on bisphosphonates:

- It is a long-term therapy to prevent the fragility fractures and it needs to be taken over long period of time, together with calcium and vitamin D supplementation (which may be prescribed) and adequate dietary intake.
- Advise the patient to stop taking the bisphosphonate and seek medical advice if they experience thigh pain, especially after 3 years of bisphosphonate treatment. This could be a sign of an atypical fracture.
- Oral bisphosphonate needs to be stopped in case of any signs or symptoms of possible oesophageal reaction like dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn. Seeking medical advice is recommended.
- Advise the person to have regular dental check-ups, before starting oral bisphosphonate treatment if they have poor dental status, and to tell their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures (due to a very rare risk of osteonecrosis of the jaw). Advise patients to inform of any dental mobility, pain or swelling.

Patient concordance:

- Patient concordance with bisphosphonates is poor due to side effects (e.g. oesophageal reaction as listed above, musculoskeletal pain, joint swelling, headache, dizziness, tiredness. See patient information leaflet for full list). To ensure the benefits are realised, it is suggested patients are assessed a month after starting treatment by the GP, practice nurse or pharmacist to check how things are going and assess concordance.
- Advise the patient that if oral doses are frequently missed, they should speak to their GP about different treatment options (also see note below about missed doses).

Administration advice for oral bisphosphonates:

- The tablet must be swallowed whole and taken with a glass of plain water (at least 200 ml). It must not be sucked or chewed because of a potential for oropharyngeal ulceration.
- It should be taken while in an upright position and they should not lie down for at least 30 minutes after taking the tablet.
- The tablet must not be taken at bedtime or before getting up in the morning.
- Once weekly preparations should be taken on the same day each week.
- **Alendronate** must be taken at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day.
- **Risedronate** should be taken at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day. Alternatively it may be taken between meals — should be taken at least 2 hours before or at least 2 hours after any food, other medicinal product, or drink (other than plain water).
- Do not take with **food, milk and dairy products, and medicinal products containing polyvalent cations** (such as calcium, magnesium, iron, and aluminium — for example antacids) as they interfere with absorption of the bisphosphonate. If taking calcium supplements, consider taking the morning dose of calcium supplement later on the day that the bisphosphonate is taken.

Missed doses:

For once-weekly oral preparations of alendronate or risedronate, advise the person:

- To take the missed tablet on the day that it is remembered.
- To continue taking one tablet once a week, on the day the tablet is normally taken.
- That two tablets should not be taken on the same day.

Helpful information:

- **The Royal Osteoporosis Society (ROS)** (www.theros.org.uk) provides support and information to people affected by osteoporosis, influences health and social care provision, and works to improve public understanding of osteoporosis.

The NHS website has a health encyclopaedia which has an article on Osteoporosis at:
https://www.nhs.uk/conditions/Osteoporosis/

APPENDIX 3. MONITORING OSTEOPOROSIS TREATMENT WITH ORAL BISPHOSPHONATES

Background

The decision to introduce osteoporosis treatment is based on fracture risk assessment, often including measurement of bone mineral density (BMD). BMD measurements are strongly predictive of fracture risk and are the basis for diagnosis of osteoporosis. BMD measurements are not, however, a good tool to assess response to most osteoporosis treatments.

Why monitor osteoporosis treatment?

First-line treatment for osteoporosis is usually with oral alendronic acid (70 mg weekly). The aim is for treatment to be taken correctly and regularly for a minimum of 5 years in the first instance and for the patient to remain calcium and vitamin D replete during this time. Treatment needs to be taken according to detailed instructions (see appendix 1).

Oral bisphosphonates are poorly absorbed with only approximately 1% of each dose being absorbed even with total compliance following instructions.

Many patients fail to persist with osteoporosis treatment while many others experience a sub-optimal response due to unintentional poor compliance or impaired absorption. Monitoring of the treatment response identifies poor response enabling treatment to be modified to improve fracture risk reduction. It has also been shown that monitoring of the treatment response may improve compliance and persistence with osteoporosis treatment.

How is treatment monitored?

It is important to check with the patient that they are following the instructions and continuing to take treatment regularly. Conventionally, osteoporosis treatment has been monitored by making periodic measurements of BMD but this is not an effective method because:

- BMD changes with osteoporosis treatment are small and slow,
- the magnitude of measurement error with BMD is similar to the change in response to treatment.

In a typical patient it is not possible to measure a significant BMD response until they have taken treatment for over 18 months. In patients with unreliable BMD measurements, it may take considerably longer. Routine BMD assessment is not, therefore, a useful technique to improve compliance with treatment as compliance problems generally arise early.

An alternative approach to monitoring is to measure biochemical markers of bone turnover (BTM). These show large and rapid changes in response to osteoporosis treatment allowing detection of a significant treatment response within a few months. It has also been shown that changes in BTM are a better predictor of reduced fracture risk than changes in BMD.

BTMs have been used in Sheffield and Nottingham to monitor osteoporosis treatment in the metabolic bone clinics for over 15 years. Until recently, experience in primary care has been limited locally and there has not been a viable automated test available. The introduction of CTx gives the opportunity to use biochemical monitoring in the community.

What is CTx?

The carboxy terminal telopeptide of collagen type I of type I collagen (CTx) is a by-product of bone resorption (during osteoclastic hydrolysis of collagen) which is released into the circulation and excreted in the urine. As a result, it is specific for the bone resorption which should be inhibited by bisphosphonates.

It is dependent on time of day and food (must be collected after an overnight fast) but, it is stable in an EDTA sample tube for up to 24 hours post collection. Serum CTx is the international standard test for

bone resorption. Within a few months of starting treatment, it is usually possible to measure a significant decrease in CTx indicating treatment response.

How is treatment response defined?
The aim is to see a response to treatment indicated by a significant decrease in bone resorption. This decrease in bone resorption correlates with a decrease in fracture risk. A significant decrease in bone turnover will be expected in patients responding to oral bisphosphonates. A reduction of the CTx concentration by more than 30% from baseline would indicate a satisfactory response to therapy. If no baseline CTx is available an empirical value of <0.30ug/L 3 months apart may indicate adherence and satisfactory efficacy of treatment.

Years of age	CTx reference range in male patients
30 to 50	<0.58 micrograms/L
51 to 70	<0.70 micrograms/L
Over 70	<0.85 micrograms/L

Years of age	CTx reference range in male patients
Up to 45	<0.57 micrograms/L
Over 45	<1.01 micrograms/L

What is the rationale for treatment if the baseline level of CTx is low?
In a patient with osteoporosis the bone turnover may not be increased but there may still be imbalance between the processes of resorption and formation leading to bone loss. It is therefore still helpful to initiate treatment with an anti-resorptive treatment such as alendronic acid to restore bone remodelling balance as treatment has been shown to reduce fracture risk regardless of the baseline level of bone turnover. If the baseline CTx level is undetectable it would be advisable to repeat the test ensuring that the patient is fasted overnight. If the CTx remains undetectable discuss with specialist prior to initiation of treatment to exclude possible causes for low bone turnover or adynamic bone disease i.e. hypoparathyroidism, post whole body irradiation and chemotherapy.

What is the significance of a very high level of CTx?
A very high CTx result indicates high bone turnover. This is usually associated with accelerated bone loss and may be an indication that there is an underlying cause of bone loss. Possible causes include secondary causes of osteoporosis, severe vitamin D deficiency / osteomalacia, malabsorption, thyrotoxicosis or, less commonly, the presence of other pathology (e.g., Paget's disease of bone, malignancy, or myeloma).

Importantly, CTx increases following a fracture or orthopedic surgery. The increase is maximal shortly after the insult but returns to baseline levels within 3-5 months. This may vary depending on the extent and nature of the fracture or surgery. Therefore, it is important to exclude recent fractures, particularly once treatment has commenced. In the absence of recent fracture or orthopedic surgery, a value greater than 1.5 to 2 times the upper limit of normal should alert the clinician to further investigation.

Chronic kidney disease may lead to a falsely raised CTx and in patients with CKD 4 and 5 the CTx may be 4- 6 times the upper reference limit. In these patients bisphosphonates are contra-indicated and this would therefore not create any problems.

What should be done if the 3 month measurement of CTx does not show a response to treatment?
1. Check compliance with treatment:
    - for the bisphosphonate and any calcium & vitamin D supplements,
    - ensure the dosing instructions are being followed correctly,
    - if poor compliance is identified, re-educate the patient, recheck compliance after 1-2 months, and then recheck CTx in 3 months' time,
    - if compliance issues cannot be reliably addressed or are due to side effects consider change in treatment,
    - if side-effects, consider weekly risedronate, if this is unsuitable or not tolerated or ineffective, consider referral,

- if difficulty with oral dosing, consider referral to specialist for parenteral preparation (zoledronic acid or denosumab).

2. Check whether the patient has sustained any fractures since the baseline measurement. If so, ensure compliance is good and consider referral.

3. If compliance is good and no fractures, undertake investigations to identify potential malabsorption or other underlying cause of poor response:
   - bone profile, PTH, vitamin D, TSH, coeliac antibodies, myeloma screen may be helpful.
   - Treat any reversible cause identified.
   - Discuss with specialist or refer if appropriate.

With thanks to Sheffield Teaching Hospital for allowing Nottinghamshire APC to adapt their document on which this appendix 2 is based.