Oxford University Hospitals NHS
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Prevention and Management of Glucocorticoid-Induced Osteoporosis in Oncology Patients Receiving Systemic Glucocorticoids for Immune Checkpoint Inhibitor- Related Adverse Events

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Table of Contents

1. Introduction

Glucocorticoid-induced osteoporosis (GIOP) is the principal cause of secondary osteoporosis[1]. Bone loss and increased fracture risk occur early after initiation of systemic glucocorticoids. These adverse effects occur in a dose-dependent manner with higher exposure elevating the risk[2-3]. The increase in fracture risk is partially independent of bone mineral density (BMD) and is observed for vertebral and non-vertebral fractures[4].

2. Scope

Patients initiated on systemic glucocorticoids and planned to receive the equivalent of ≥7.5 mg/day prednisolone for >3 months require baseline bone health assessments. **This therefore applies to all patients with moderate to severe immune checkpoint inhibitor (ICI)-mediated toxicity commenced upon a tapering course of glucocorticoids at a starting dose equivalent to ≥ 1mg/kg/day prednisolone.**

Management of direct ICI-induced skeletal immune-related adverse events (irAEs) and non-skeletal toxicity of systemic glucocorticoids are beyond the scope of this guideline.

3. Aim

The purpose of this guideline is to ensure:

3.1 Completion of baseline bone health assessments
3.2 Consideration of measures to mitigate against GIOP

4. Definitions

4.1 **Dual X-ray Absorptiometry (DXA): '**A method of measuring bone density based on the proportion of a beam of photons that passes through the bone. Results are expressed as a T score'[5].

4.1.1 **DXA with Vertebral Fracture Assessment (VFA):** Describes lateral views of the thoracic and lumbar spine acquired on DXA scanners to diagnose vertebral fractures[6].

4.2 **Fracture Risk Assessment Tool (FRAX®):** Integrates clinical risk factors with or without BMD at the femoral neck to calculate the 10-year probability of hip and major osteoporotic fracture (MOF).

4.2.1 FRAX® clinical risk factors include: Age, sex, weight, height, previous fracture, parent fractured hip, current smoker, rheumatoid arthritis, alcohol ≥ 3 units/day, and secondary osteoporosis [Section 4.5].

4.2.2 The updated version of the online FRAX® model: https://www.fraxplus.org/calculation-tool[7-9]

4.2.3 FRAX® computations assume an average exposure equivalent to ≥5 mg/day prednisolone over 3 months. For high doses (>7.5 mg daily), probabilities are augmented by approximately 15% and 20% for MOF and hip fractures respectively[10].

4.2.4 FRAXplus® revises the probability result derived from conventional FRAX® estimates to account for higher than average glucocorticoid exposure[9] but given there is a fee for this adjustment it is not recommended.

4.3 **MOF:** Hip, clinical spine, distal forearm, or proximal humerus fracture[11].

4.4 **Osteonecrosis of the Jaw (ONJ):** Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks in the absence of prior jaw irradiation, in patients with a current or previous history of bisphosphonate or denosumab use[12-13].

4.5 **Secondary Osteoporosis:** 'Osteoporosis caused by certain medical conditions or medications that can cause bone loss, increase fracture risk, directly or indirectly affect bone remodelling or interfere with the attainment of peak bone mass in younger individuals.'[14] Secondary causes include:

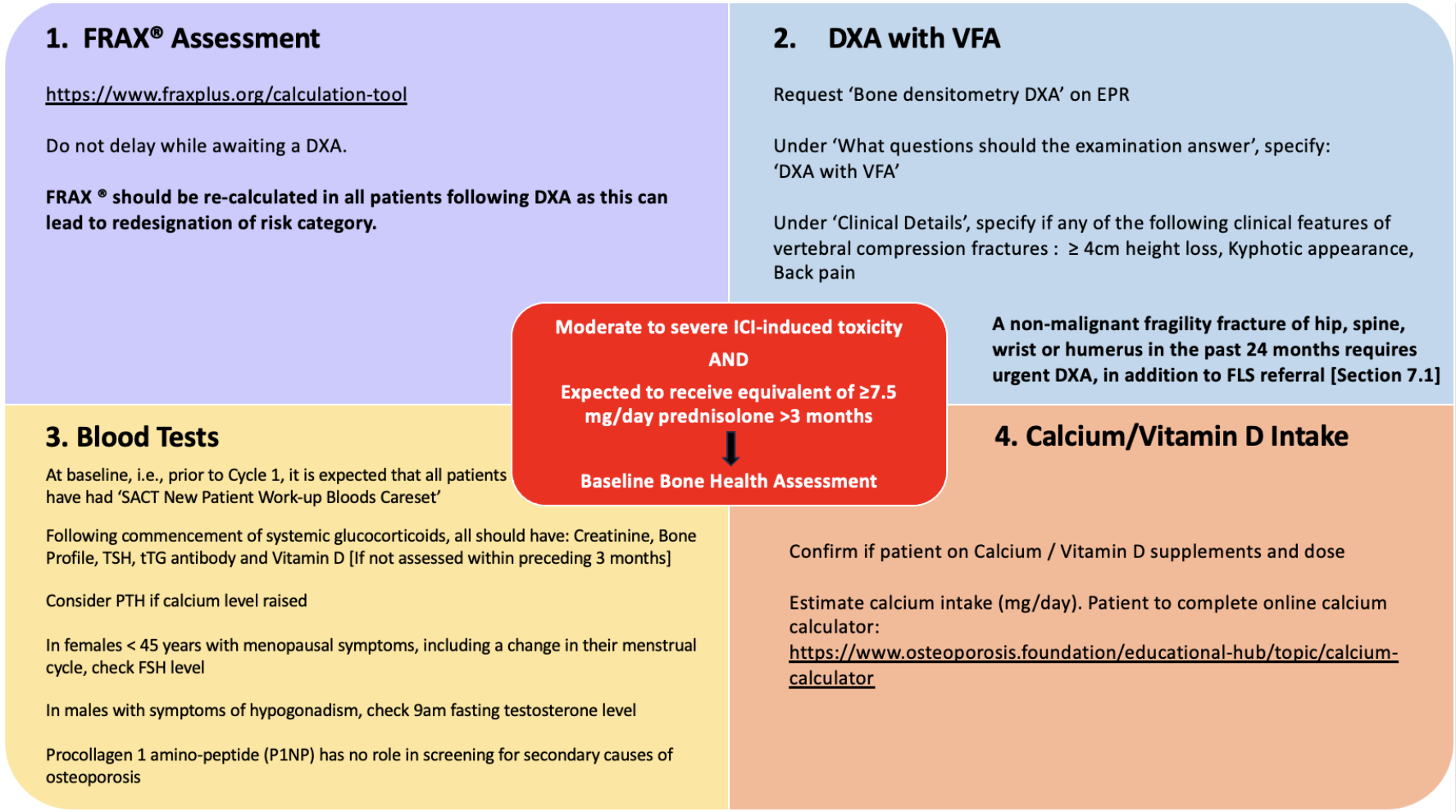
4.5.1 Type I (insulin dependent) diabetes
4.5.2 Long-standing untreated hyperthyroidism
4.5.3 Untreated hypogonadism/premature menopause (<45 years)
4.5.4 Chronic malnutrition/malabsorption
4.5.5 Chronic liver disease
4.5.6 Non-dialysis chronic renal failure (i.e., CKD 3a – 5)
4.5.7 Osteogenesis imperfecta in adults[15]

5. Baseline Bone Health Assessment

5.1 The majority of oncology patients requiring systemic glucocorticoids for irAEs are initiated upon treatment in acute-care settings. Acknowledging the clinical pressures and time constraints in such environments, it is recommended that bone health is addressed by the patient's tumour site team within two-weeks of glucocorticoid commencement. All patients should be provided with the relevant Royal Osteoporosis Society (ROS) leaflet: https://theros.org.uk/information-and-support/osteoporosis/causes/steroids/[16]

5.2 A baseline bone health assessment comprises four components [Figure 1].

Figure 1 – Baseline Bone Health Assessment



6. Prevention and Management of GIOP

6.1 After entering clinical risk factors +/- BMD at femoral neck on FRAX® [https://www.fraxplus.org/calculation-tool], click 'Calculate', followed by 'View NOGG guidelines'[15]. This will generate graph(s) depicting fracture risk and 'Intervention Thresholds'. Figure 2 illustrates management according to the level of fracture risk**. Irrespective of risk level, if any of the following criteria are met, oral bisphosphonates should be started at the same time as glucocorticoid therapy without waiting for DXA which should follow later (with FRAX® re-calculation):**

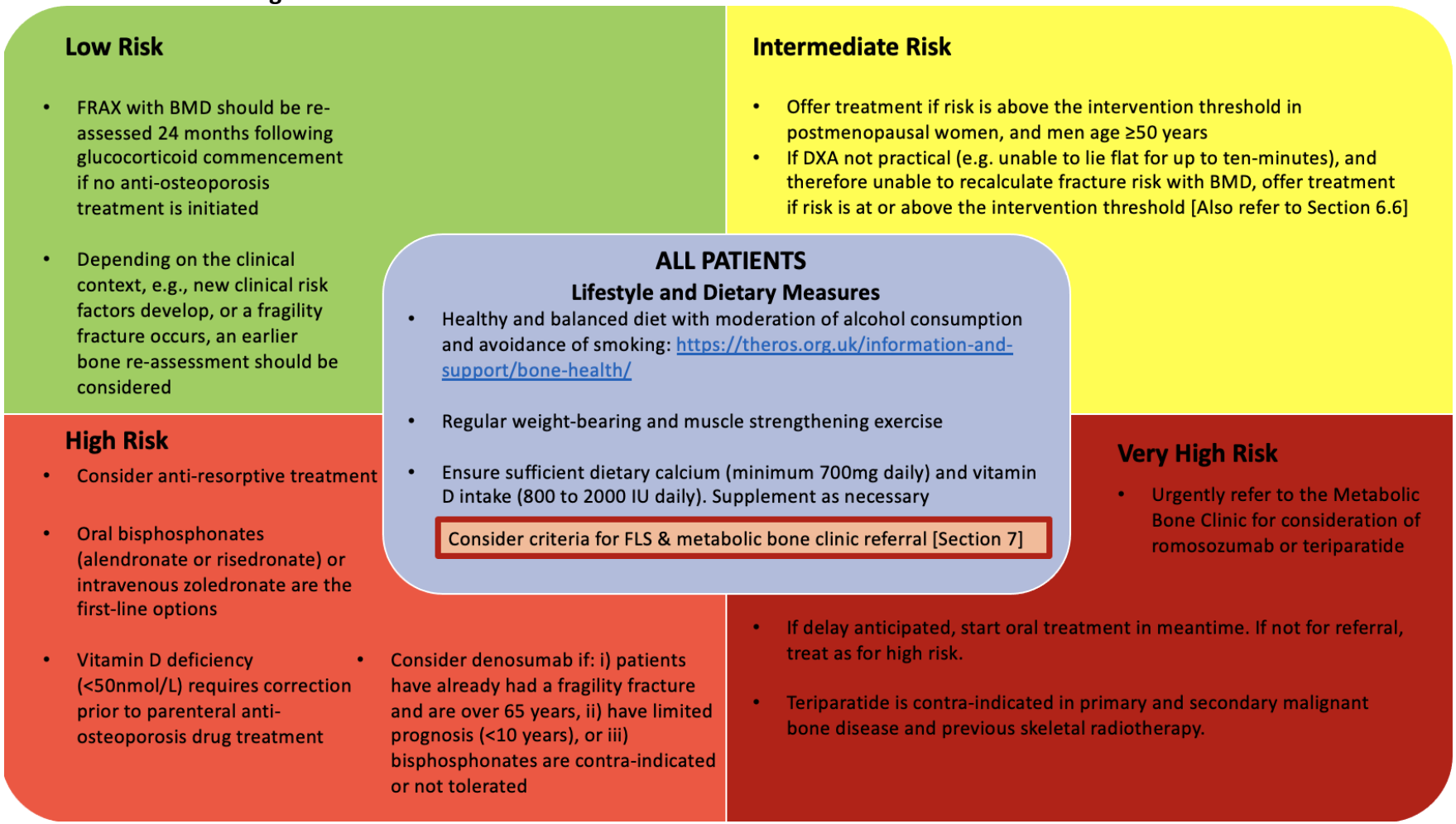
6.1.1 Prior fragility fracture,

6.1.2 Women age ≥70 years,

6.1.3 Postmenopausal women, and men age ≥50 years, prescribed high doses of glucocorticoids, i.e., equivalent to ≥7.5 mg/day prednisolone for >3 months (**N.B., this applies to all patients commenced upon a tapering course of glucocorticoids at a starting dose equivalent to ≥1mg/kg/day prednisolone**).

6.1.4 Postmenopausal women, and men age ≥50 years, with a FRAX probability of major osteoporotic or hip fracture exceeding the intervention threshold[15].

Figure 2 - Prevention and Management of GIOP



6.2 The National Osteoporosis Guideline Group (NOGG) do not routinely advise DXA in low-risk patients when FRAX® is performed in the absence of BMD[15]. However, as outlined in figure 1, DXA with VFA is recommended in all patients who fulfil criteria for a baseline bone health assessment. The rationale for a baseline DXA is that FRAX® does not factor glucocorticoid *dose* [Section 4.2.3], and therefore will generally underestimate the fracture risk in patients with irAEs receiving high doses of glucocorticoids.

6.3 FRAX® in the absence of BMD classifies MOF risk as low, intermediate, high, or very high [Appendix 1].

6.4 FRAX® with BMD designates the risks of MOF and hip fracture within 3-categories: Low, high, or very high [Appendix 2]. If there is discordance between the risk categories identified by the two probabilities, the highest risk category should be adopted to guide intervention[15].

6.5 The benefits of bone protective therapies on BMD and fracture risk are supported by high level evidence [Appendix 3].

6.6 Bone protective therapy may be appropriate in premenopausal women and men <50 years, for example if there is history of previous fragility fracture[15]. In these age groups, consider referral to the metabolic bone clinic [Section 7.2.2]. Caution is advised when prescribing bisphosphonates in women of reproductive potential. Bisphosphonates are incorporated into bone and the terminal half-life is up to 10 years, with a lack of foetal safety data[17]. Denosumab is not recommended in patients <65 years with an expected survival of >10 years because long-term use data is limited.

6.7 Intravenous and oral bisphosphonates are prescribed for at least 3 - 6 and 5 - 10 years respectively [Appendix 4, 5].

6.8 Regularly review patients' tolerance of, and adherence to oral bisphosphonates. Adherence should assess that:

- **6.8.1** Tablets are taken after an overnight fast and at least 30 minutes before the first food or drink (other than water) of the day or any other oral medications[15].
- **6.8.2** Calcium containing supplements are not taken within 4 hours of the bisphosphonate as this may result in reduced absorption of the bisphosphonate[18].
- **6.8.3** Tablets are swallowed whole with a glass of plain water (~200ml) while sitting or standing in an upright position.
- **6.8.4** Patients do not lie down for 30 minutes after taking the tablet.

6.9 Common side effects of alendronate and risedronate include: upper gastrointestinal (GI) symptoms, change in bowel habit, headaches and musculoskeletal pain[15].

6.10 Upper GI adverse effects, such as nausea, dyspepsia, and abdominal pain, are common in the first month of treatment and often improve[18]. Patients should be advised to stop the bisphosphonate and seek medical attention if they develop any symptoms of oesophageal irritation including: difficulty or pain upon swallowing, chest pain, or new or worsening heartburn[19]. If symptoms are mild, continue the oral bisphosphonate. If moderate/severe or dysphagia is reported, stop and consider alternative anti-osteoporosis medications.

7 Criteria for Specialist Referral

7.1 Fracture Liaison Service (FLS)

7.1.1 A non-malignant fragility fracture of hip, spine, wrist or humerus within the last 24 months requires referral to the local FLS. Such fragility fractures may be incidental radiological findings. For example, acute vertebral compression fractures may be identified on DXA with VFA.

7.1.2 The FLS will recommend an individualised care plan for secondary prevention of fragility fractures and works in liaison with: Primary care, falls prevention service, metabolic bone clinic, and physiotherapists.

7.1.3 Referral to the local FLS is via EPR 'Communicate'. Under 'Pool', send to inbox 'Fracture Prevention Services'.

7.2 Metabolic Bone Clinic

7.2.1 Any of the below features should prompt referral to the metabolic bone clinic for consideration of romosozumab or teriparatide:

7.2.1.1 FRAX® output of very high fracture risk,

7.2.1.2 Lowest BMD T Score ≤-3.5,

7.2.1.3 ≥3 fragility fractures as an adult and lowest BMD T score ≤-3. **Note patients who also fulfil 7.1.1 should instead be referred to the FLS**[15].

7.2.2 Referral to the metabolic bone clinic is via EPR 'Communicate'. Under 'Staff', send to inbox 'Access Team Metabolic Bone NOC Rheumatology OP'.

8 Rare Adverse Effects of Long-term Bisphosphonate and Denosumab Treatment

8.1 Rare but serious adverse effects are atypical femoral fractures (AFFs) and ONJ. Osteonecrosis of the external auditory canal is very rare.

8.2 AFFs

8.2.1 Advise patients to report unexplained thigh, groin, or hip pain. If such symptoms develop, first-line imaging is full length x-ray of the femur. MRI is recommended when x-ray is negative.

8.2.2 If an AFF is identified, image the contralateral femur.

8.2.3 If an incomplete AFF is detected, urgently refer to the orthopaedic trauma clinic for review within 24-hours (On-Call Trauma SpR: Bleep 1222). Discontinue bisphosphonate or denosumab treatment and advise to non-weight bear. Patients will thereafter require referral to the metabolic bone clinic to inform management of future bone health [Section 7.2.2][15].

8.3 ONJ

8.3.1 Comprehensive guidelines on 'Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw' have been developed by the Scottish Dental Clinical Effectiveness Programme[20].

8.3.2 Risk factors for ONJ include: cumulative anti-resorptive drug dose, concurrent systemic glucocorticoids, smoking, chemotherapy, poor oral hygiene, dentoalveolar surgery, mucosal trauma, dental infection, untreated periodontal disease, and a previous episode of ONJ[15,20].

8.3.2 In patients receiving anti-resorptive therapy for osteoporosis, the incidence of ONJ is <0.05%. The incidence is greater (<5%) with the higher doses of bisphosphonates or denosumab that are used to treat patients with malignant bone disease[21].

8.3.3 If using osteoporosis doses, clinicians should assess for poor dentition including black, loose and broken teeth. If present, timely dental referral should be pursued before anti-resorptive drug administration[12,15,20], acknowledging that anti-resorptive treatment should be initiated as soon as possible following a fragility fracture[15].

Other patients receiving anti-resorptive therapy for osteoporosis do not routinely require a formal dentist review. This contrasts with all patients receiving bisphosphonates or denosumab for the management of cancer, who should preferably undergo a dental check-up prior to treatment due to the increased anti-resorptive drug dose and risk of ONJ[12,20-21].

8.3.4 Encourage patients to maintain good oral hygiene with effective brushing for 2 minutes twice a day, interdental cleaning, and use of fluoride toothpaste and mouthwash[20]. Gums should never bleed during brushing. Effective brushing and personalised preventative dental regimes may be taught by a local dental hygienist.

8.3.5 To optimise oral health, advise: A well-balanced diet, smoking cessation, limiting alcohol intake, regular dental check-ups, and promptly reporting any oral symptoms such as dental mobility, pain, or swelling[12,20].

8.3.6 Ideally where possible, invasive dental procedures should be minimised during anti-resorptive treatment. However, if necessary, they can be performed safely and successfully in most patients[15]. Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone-impacting treatments specifically to reduce the risk of ONJ.

8.3.7 There is no evidence that ONJ risk will be reduced if bisphosphonates are stopped, either temporarily or permanently prior to invasive dental procedures, since the drugs have a prolonged elimination half-life. An acceptable management option for patients with osteoporosis treated with six monthly denosumab is to delay non-urgent invasive dental treatment in an asymptomatic tooth until the month prior to the next scheduled drug administration. Denosumab may be resumed following invasive dental work once the soft tissues/extraction socket have healed. Liaise with the patient's dental practitioner to coordinate care[20].

8.3.8 Patients should be provided with the following ROS leaflet: https://theros.org.uk/information-and-support/osteoporosis/treatment/health-risks/osteonecrosis-of-the-jaw/#:~:text=Osteonecrosis%20of%20the%20jaw%20(ONJ)%20is%20a%20very%20rare%20side,It%20doesn't%20happen%20often.[22]

8.4 Osteonecrosis of the External Auditory Canal

8.4.1 Occurs predominantly with long-term therapy (2 years or longer).

8.4.2 It should be considered in patients with ear symptoms such as pain and discharge or chronic ear infections[23].

9. Monitoring Compliance

Compliance with the document will be monitored in the following ways:

Aspect of compliance or effectiveness being monitored	Monitoring method	Minimum Standard	Responsibility for monitoring (job title)	Group or Committee that will review the findings and monitor completion of any resulting action plan
Bone health Assessment	Bi-annual consecutive audit of 20 patients EPR records commenced glucocorticoids for irAEs	80% have documented bone assessment history completed	Oncology Registrar	Multi-disciplinary Bone Health Working Group
Bone health recommendation	Bi-annual consecutive audit of 10 patients EPR records	80% of patients meeting intervention threshold are recommended appropriate bone protective therapy	Oncology Registrar	Multi-disciplinary Bone Health Working Group
Bone health advice	Bi-annual consecutive audit of 10 patients EPR records	80% of records signpost patients to ROS resources	Oncology Registrar	Multi-disciplinary Bone Health Working Group

10. Review

This policy will be reviewed in 3 years, as set out in the *Policy for the Development and Implementation of Procedural Documents.*

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12. Equality Analysis

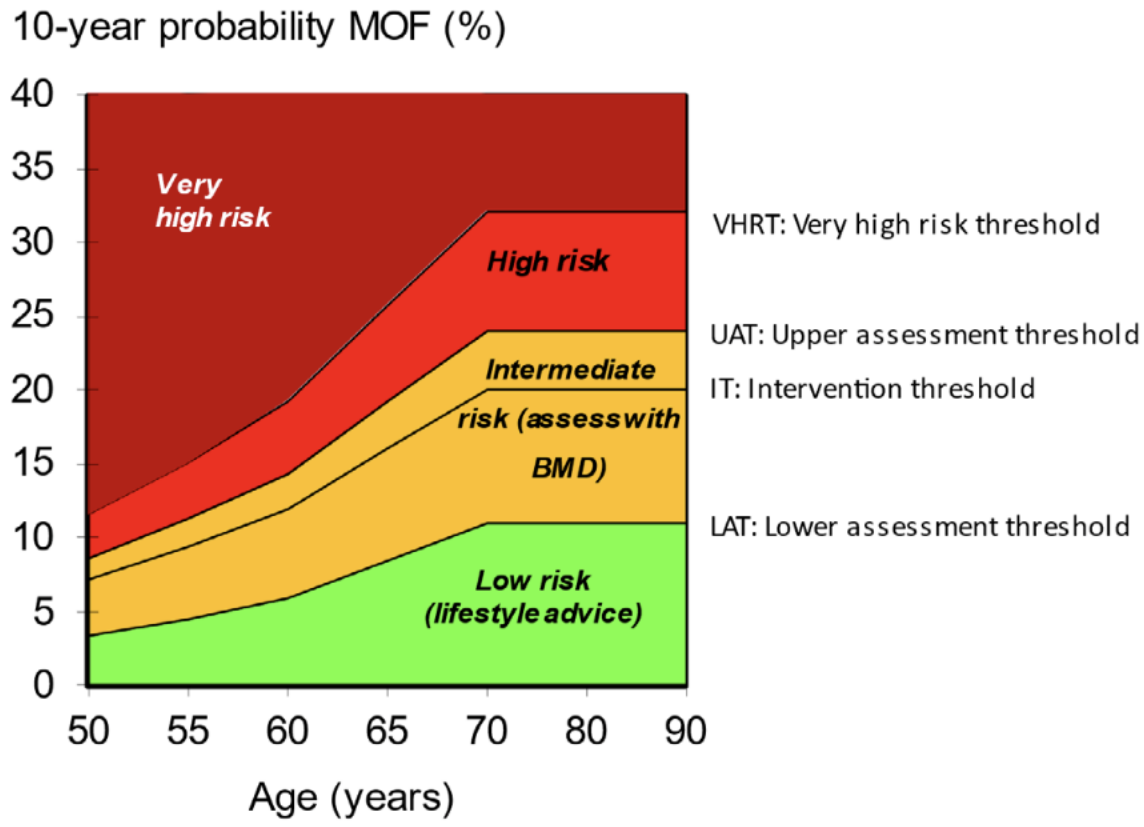
12.1 As part of its development, this policy and its impact on equality, diversity and human rights has been reviewed, an equality analysis undertaken, and no adjustments are required.

13. Document History

Date of revision	Version number	Reason for review or update
28/05/2024	2	Updated: Baseline Bone Health Assessment, Prevention and Management of GIOP, and information on acute vertebral compression fractures. Addition of 'Definitions' and information on rare adverse effects of long-term bisphosphonate and denosumab treatment.
25/07/2024	3	Updated: Scope, Definitions, Baseline Bone Health Assessment, Prevention and Management of GIOP, Rare Adverse Effects of Long-term Bisphosphonate and Denosumab Treatment, and Monitoring Compliance. Addition of: 'Criteria for Specialist Referral'.

Appendix 1

NOGG Assessment, Intervention and Risk Thresholds for MOF Probability in the UK with the use of FRAX® in the Absence of BMD[15]



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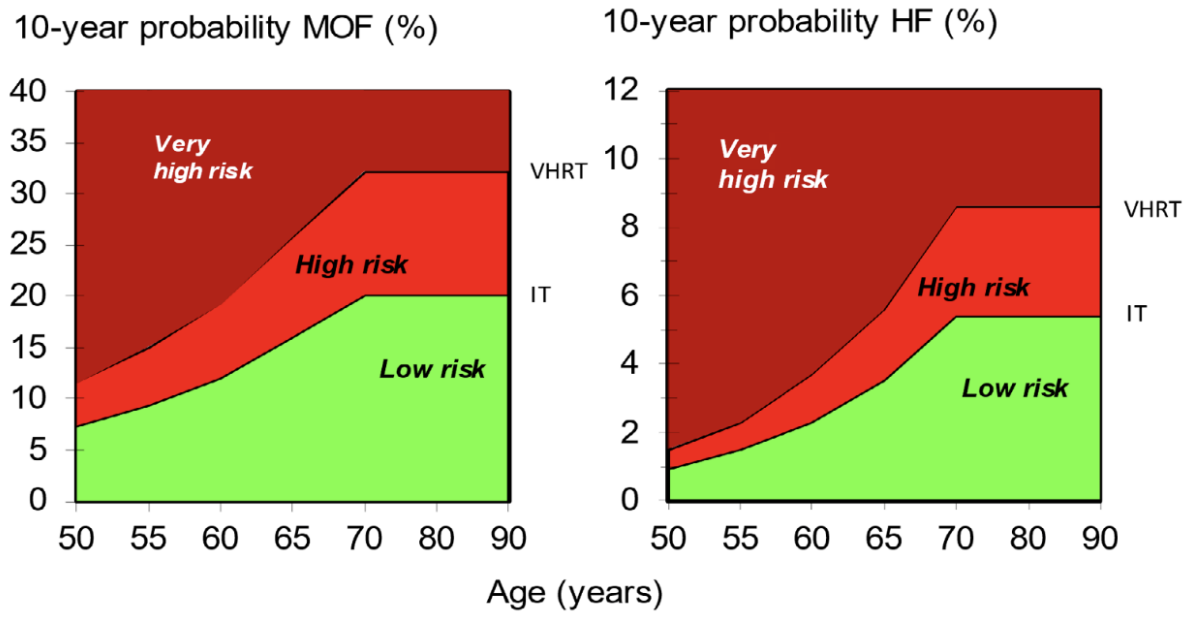
Appendix 2

NOGG Thresholds for Intervention using MOF and Hip Fracture Probabilities in the UK according to FRAX® with BMD Input[15]



HP; Hip fracture
IT; Intervention threshold
VHRT; Very high-risk threshold

Appendix 3

Effects of Bone Protective Therapies on BMD and Fracture Risk in GlOP[15]

Bone protective therapy	Spine BMD	Hip BMD	Vertebral fracture	Non-vertebral fracture	Evidence of superiority for spine and/or hip BMD
Alendronate	Ib	Ia	Ia	Ia	Inferior to teriparatide (Ib)
Risedronate	Ib	Ia	Ia	NAE	Inferior to zoledronate (Ia)
Zoledronate	Ib	Ib	Ia	NAE	Superior to risedronate (Ib)
Denosumab	Ib	Ia	Ia	NAE	Superior to bisphosphonates (IIa)
Teriparatide	Ib	Ib	Ia	Ia	Superior to alendronate (Ib)

NAE; No available evidence.

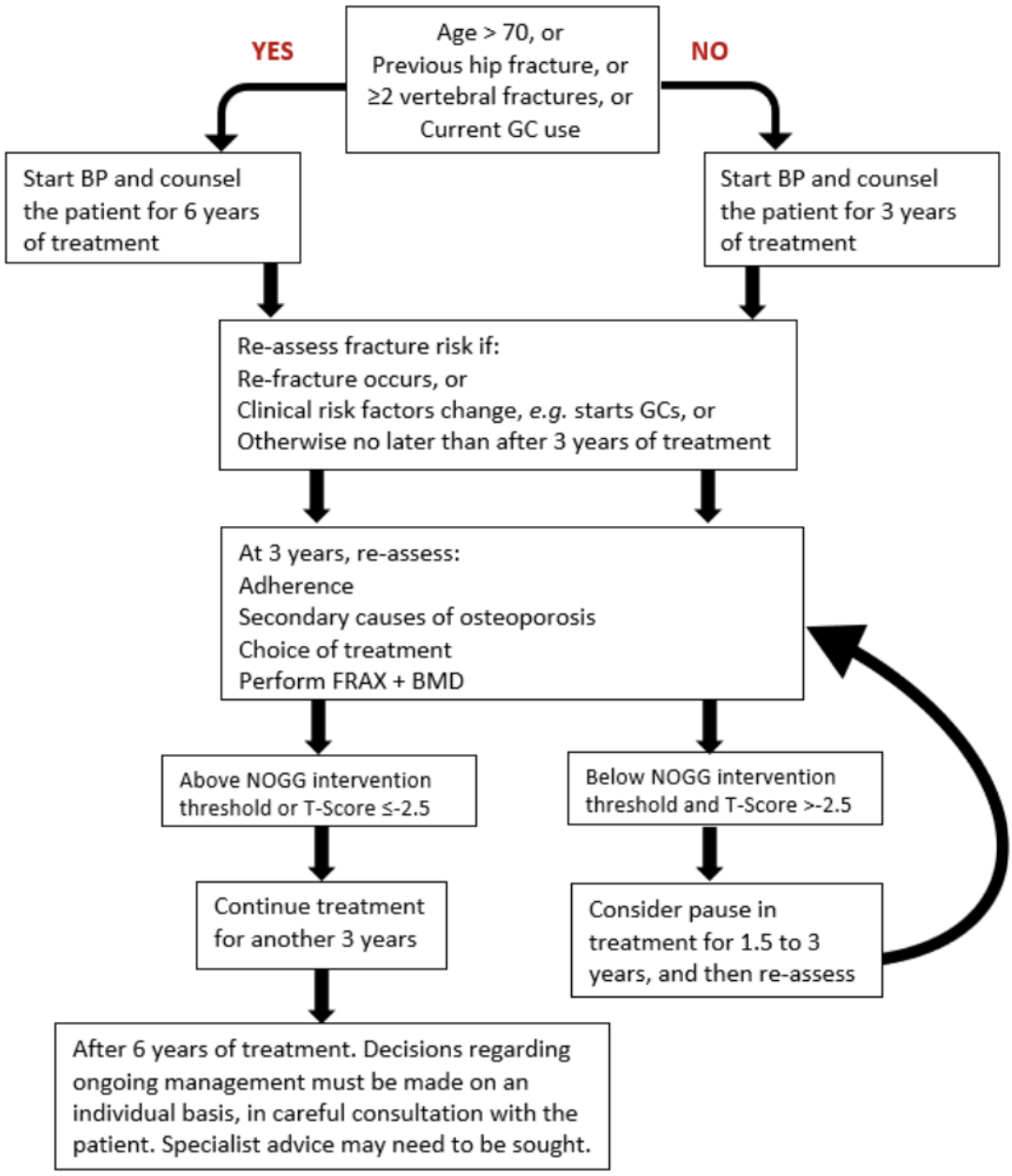
Levels of evidence for studies of intervention:

Ia from systematic review and meta-analysis of randomised controlled trials (RCTs)

Ib individual RCT(s) (with narrow confidence intervals)

Appendix 4

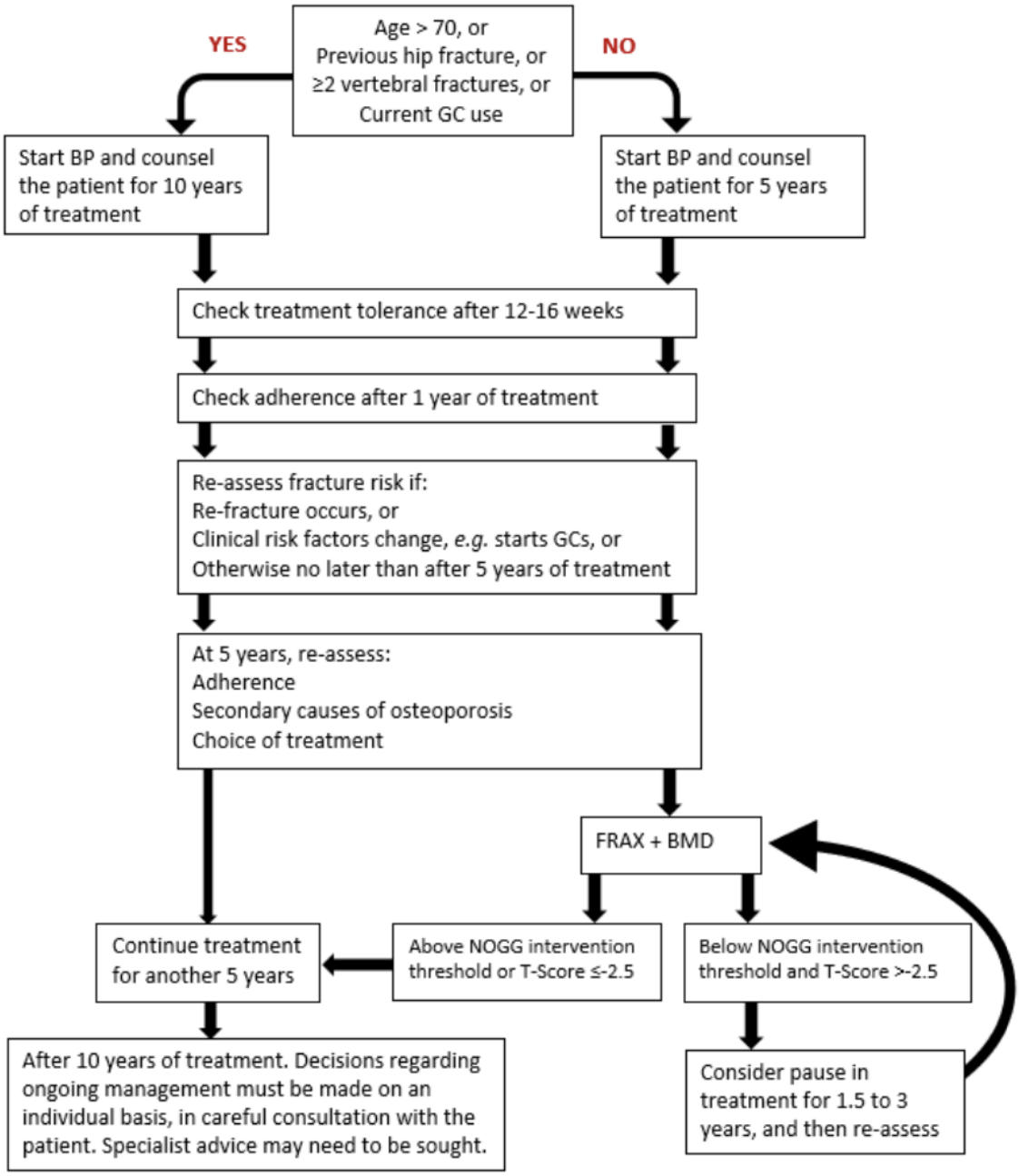
Intravenous Bisphosphonates: Algorithm for Long Term Treatment and Monitoring[15]



GC: Glucocorticoids (oral ≥7.5 mg prednisolone/day or equivalent). BP: bisphosphonate

Appendix 5

Oral Bisphosphonates: Algorithm for Long Term Treatment and Monitoring[15]



GC: Glucocorticoids (oral ≥7.5 mg prednisolone/day or equivalent). BP: bisphosphonate