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National Osteoporosis Guideline Group • UK

Clinical guideline for the prevention and treatment of osteoporosis

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Contents

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In October 2021 NICE reaccredited the process used by the National Osteoporosis Guideline Group to produce this clinical guideline for the prevention and treatment of osteoporosis.

The key to wording used in this guideline

The recommendations made in this guideline have been systematically graded, according to the quality of information available, to indicate the level of evidence on which recommendations are based. There are two strengths of recommendation made in this guideline, informed by the balance between desirable and undesirable effects, the quality of the evidence-base, values and preferences, and resource allocation within the UK health community. Understanding the wording is important when deciding how to accommodate these recommendations in your clinical practice.

Strong recommendations

These begin with action verbs like **'advise', 'assess', 'conduct', 'measure', 'offer', 'plan', 'refer', 'review', 'start'** and similar.
A strong recommendation applies where the clinician reasons that most patients ought to receive the intervention, or where adherence to the recommendation could be used as a performance or quality indicator and that deviation from this recommendation would prompt documentation of a clinician's rationale for doing so.

Conditional recommendations

These begin with the term '**consider**'.
A conditional recommendation applies where the clinician examines the evidence within the wider health and social context and discusses the choices with the patient, taking into account the patient's values and preferences, or where documentation of the discussion of the pros and cons of an intervention is the indicator of quality, rather than the course of action itself.

Further information is provided in Appendix 3 and 4.

The National Osteoporosis Guideline Group, supported by:

- Association for Clinical Biochemistry and Laboratory Medicine
- Bone Research Society
- British Geriatrics Society
- British Orthopaedic Association
- British Orthopaedic Research Society
- British Menopause Society
- British Society for Rheumatology
- European Calcified Tissue Society
- European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
- International Osteoporosis Foundation
- Osteoporosis 2000
- Osteoporosis Dorset
- Primary Care Rheumatology and Musculoskeletal Medicine Society
- Royal College of Physicians
- Royal Osteoporosis Society
- Royal Pharmaceutical Society
- Society for Endocrinology
- The Nutrition Society

Summary of main recommendations

This guideline summary addresses the assessment, diagnosis and current treatments for osteoporosis, including recommendations to prevent fragility fractures. It applies to postmenopausal women, and to men age 50 years or older.

Concerning assessment of fracture risk in postmenopausal women, and men age ≥50:

Conduct a FRAX assessment in people with a clinical risk factor for fragility fracture.

1. **Measure BMD in people with intermediate fracture risk by FRAX** (amber) to refine the estimate of 10-year risk.
2. **Measure BMD in people with high and very high fracture risk by FRAX** (red) to guide drug choice and provide a baseline for BMD monitoring.
3. **Consider imaging to look for a vertebral fracture in people with acute onset back pain who have risk factors for osteoporosis**, and/or in people with a history of ≥4cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤-2.5.
4. **Assess falls risk in patients with osteoporosis and/or fragility fractures and offer those at risk an exercise programme** to improve balance and muscle strength.

Regarding drug treatment to prevent fractures in postmenopausal women, and men age ≥50:

5. **Offer drug treatment to people at high and very high risk of fracture.**
6. **If BMD measurement is not practical** (e.g. **due to frailty), use the online NOGG intervention thresholds based on FRAX, to guide treatment decisions.**
7. **Consider, particularly in older people, drug treatment in those with a prior and/or recent fragility fracture.**

When selecting drug treatments to prevent fractures in postmenopausal women, and men age ≥50:

8. **Consider the level of fracture risk, any additional clinical risk factors, patient choice, and the cost-effectiveness of treatment,** when deciding on a particular drug treatment.
9. **Start treatment promptly following a fragility fracture**, because risk of re-fracture is highest immediately after a fracture and risk remains elevated.
10. **Consider referral of very high risk patients to an osteoporosis specialist in secondary care**, for assessment and consideration of parenteral treatment (some may need first-line anabolic drug treatment, especially if multiple vertebral fractures). Indications for specialist referral include the presence of important risk factors, including a recent vertebral fracture [within the last 2 years], ≥2 vertebral fractures [whenever they have occurred], BMD T-Score ≤-3.5, treatment with high dose glucocorticoids [≥7.5 mg/day of prednisolone or equivalent over 3 months]; the presence of multiple clinical risk factors, particularly with a recent fragility fracture indicating high imminent risk of re-fracture; or other indicators of very high fracture risk.
11. **In other patients for whom treatment is indicated, offer antiresorptive therapy with oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate.**
12. **Consider alternative treatment options if these first-line bisphosphonates are unsuitable or not tolerated**; denosumab, ibandronate, hormone replacement therapy, raloxifene or strontium ranelate.
13. **Following treatment with teriparatide or romosozumab**, start alendronate, zoledronate or denosumab without delay.

When postmenopausal women, and men age ≥50, have started drug treatment:

14. **Regularly review patients' tolerance of, and adherence to, oral drug treatments**.
15. **Remember long-term treatment is often required**, because osteoporosis is a long-term condition for which there is currently no cure.
16. **Plan to prescribe oral bisphosphonates** for at least **5 years, or intravenous bisphosphonates for at least 3 years and then re-assess fracture risk.** Longer durations of treatment will be needed in those who are older (age ≥70 years), have had a hip or vertebral fracture, are on high-dose oral glucocorticoids [≥7.5 mg/day of prednisolone or equivalent over 3 months], or have a further fragility fracture during osteoporosis treatment. In lower risk patients, a temporary treatment pause of 18 to 36 months can be considered after 5 years' oral bisphosphonate or 3 years' intravenous bisphosphonate (see clinical flow-charts on p.35 and p.36).
17. **Before starting denosumab, ensure a long-term personalised osteoporosis management plan** is in place.
18. **Do not stop denosumab treatment without a plan** for subsequent anti-resorptive therapy, where renal function permits.
19. **Repeat fracture risk assessment after any new fracture**, regardless of when this occurs.
20. **Reassess fracture risk 18 months to 3 years after pausing drug treatment.**

When postmenopausal women, and men age ≥50, are treated with oral glucocorticoids:

21. **If starting ≥7.5 mg/day prednisolone or equivalent for the next 3 months, start bone protective treatment at the same time** (without waiting for a DXA scan, which can follow later).
22. **Offer antiresorptive therapy with oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate**, and in those at very high risk of vertebral fracture refer for consideration of anabolic treatment.
23. **Consider denosumab as an alternative treatment option.**

When advising on lifestyle and dietary measures:

24. **Recommend a healthy, balanced diet, moderation of alcohol consumption and avoidance of smoking.**
25. **Ensure a sufficient dietary calcium and vitamin D intake and supplement these as necessary.**
26. **Encourage a combination of regular weight-bearing and muscle strengthening exercise.**

Regarding fracture prevention services:

27. **Patients who sustain a fragility fracture should have access to a multidisciplinary, coordinator-based Fracture Liaison Service (FLS)** which enables timely fracture and falls risk assessment, investigation, treatment, and monitoring.
28. **Ensure that diagnostic imaging services routinely evaluate the spine in all imaging** of postmenopausal women, and men age ≥50 years, in which the spine is visualised, and report vertebral fractures using standardised methods.

When a postmenopausal woman, or a man age ≥50 has a symptomatic osteoporotic vertebral fracture:

29. **Consider referral to an exercise programme** which provides progressive muscle strengthening activity, including back extensor muscle strengthening and/or endurance exercise.
30. **Investigate for underlying causes of fragility fracture.**
31. **Start treatment promptly** to reduce the risk of further fractures.

The evidence presented in this guideline underpins a further series of recommendations made for leaders and commissioners of healthcare services, as well as criteria for audit and quality improvement in primary and secondary care settings.

Section 1

Scope of this guideline

a. This updated guideline has been prepared with the support of the societies listed to provide guidance on prevention and treatment of osteoporosis with the overarching aim of reducing fragility fracture risk. This guideline updates previous National Osteoporosis Guideline Group (NOGG) guidance [1-3].

b. The scope of the guideline is to review the assessment and diagnosis of osteoporosis, the therapeutic interventions available and the approaches for the prevention of fragility fractures, in postmenopausal women, and in men aged 50 years or older. This focus is chosen as fragility fractures and osteoporosis are uncommon in premenopausal women, and men younger than 50 years and therefore when these occur patients need thorough investigation for secondary causes of osteoporosis, and careful consideration of treatment options. Specialist referral is usually required.

c. This NOGG guidance has appraised the current evidence-base to inform these updated recommendations. The aim of the guideline is to provide clinically appropriate recommendations which integrate available evidence on clinical efficacy, effectiveness and safety. This contrasts with, but complements, the remit of the National Institute for Health and Care Excellence (NICE), which focuses principally on establishing criteria for cost effectiveness. Cost effectiveness analyses are generally supportive for treatment guided by clinical effectiveness thresholds, rather than defining intervention thresholds per se [4]. The NOGG recommendations have been previously demonstrated to be cost-effective and at the time of writing, NICE's appraisal of romosozumab is awaited, with preliminary evidence of its cost-effectiveness established [5].

d. The guideline has been prepared by a writing group (Appendix 1) and has been approved after consultation with stakeholders (Appendix 2).

e. The guideline is intended for all healthcare professionals involved in the prevention and treatment of osteoporosis and fragility fractures. This includes primary care practitioners, allied health professionals and relevant specialists in secondary care including rheumatologists, gerontologists, gynaecologists, endocrinologists, clinical biochemists, and orthopaedic surgeons. The guideline includes recommendations for training in osteoporosis care.

f. The guideline is supported by a series of Frequently Asked Questions (FAQs) available on the NOGG website.

g. The conclusions and recommendations in the document are systematically graded, according to the quality of information available, to indicate the level of evidence on which recommendations are based. The grading methodology is summarised in Appendix 3. Where available, systematic reviews, meta-analyses and randomized controlled trials have been used to provide the evidence base. The evidence base has been updated using PubMed to identify systematic reviews and meta- analyses from July 2016 to Sept 2020. The quality of systematic reviews and meta-analyses used in the formulation of recommendations was assessed using AMSTAR2 (Appendix 4). The recommendations in this guideline were agreed by the National Osteoporosis Guideline Development Group.

h. It is recommended that the guideline is reviewed at an interval of not more than 5 years. Earlier revision may be necessary if new drugs are approved or there is a major change to the evidence base. Minor changes, for example extension of an indication, new safety data or changes to the Summary of Product Characteristics (SPC) of an intervention, will be made on the website when and if appropriate.

i. This guideline provides a framework from which local management protocols should be developed to provide advice for healthcare professionals. Implementation of this guideline should be audited at a local and national level.

j. The recommendations in the guideline should be used to aid management decisions but do not replace the need for clinical judgment in the care of individual patients in clinical practice.

Section 2

Introduction to osteoporosis and fragility fractures

a. The conceptual definition of osteoporosis was made by the World Health Organization (WHO) in 1994 as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [6]. Since microarchitectural deterioration could not be measured clinically, the operational description was based on a bone mineral density (BMD) T-Score of ≤-2.5. Over the years this was adopted as a clinical definition; however, the limitations of focusing on a BMD-based definition alone have since become clear. BMD is now viewed as one, albeit very important, risk factor to be considered when assessing fracture risk which is now viewed as the principal necessity.

b. The clinical significance of osteoporosis lies in the fractures that arise. Approximately one in two adult women and one in five men will sustain one or more fragility fractures (a low trauma fracture sustained from a fall from standing height or less) in their lifetime [7]. In the UK, the prevalence of femoral neck BMD T-Score ≤-2.5, in those aged 50 years and older, is 6.8% in men and 21.8% in women [8]. However, the majority of people who sustain a fragility fracture will have a femoral neck BMD T-Score above -2.5, reflecting the contribution of many other factors, besides BMD, to fracture risk [9-11]. Fall-related risk factors add significantly to fracture risk and often overlap with risk factors for osteoporosis, hence the need for integrated fall and fracture services.

c. Currently in the UK, approximately 549,000 new fragility fractures occur each year, including 105,000 hip fractures, 86,000 vertebral fractures, and 358,000 other fractures (i.e., fractures of the pelvis, ribs, humerus, forearm, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures); 33% are sustained by men [8,12,13]. Such fractures cause severe pain, disability, and reduction in quality of life [14,15]. In the UK, fragility fractures are estimated to account for 579,722 DALYs (Disability Adjusted Life Years) lost, largely driven by years lived with disability. This equates to 24 DALYs per 1000 people aged over 50 years, which is comparable to the DALYs lost from dementia [8].

d. Costs of fragility fractures to the National Health Service (NHS) exceed £4.7 billion per annum, of which £2.6 billion is directly incurred after an incident fracture (£1.1 billion for hip fractures alone [16]), with more than £1.7 billion attributable to institutional care costs post-fracture (estimated for 2017) [8]. Total direct costs for 2019 were £5.4 billion accounting for 2.4% of healthcare spending [17].

e. Common sites of fragility fracture include the vertebral bodies, hip, distal radius, proximal humerus and pelvis. Hip fracture is the most common reason for emergency anaesthesia and surgery in older people. It is also the most common cause of death following a fall. After hip fracture the mean hospital length of stay is 20 days, accounting for half a million hospital bed days used each year, with 3,600 hospital beds (3,159 in England, 325 in Wales and 133 in Northern Ireland) occupied at any one time by patients recovering from hip fracture [18,19]. Loss of independence is common following a hip fracture with only 52% living in their own home after 120 days [12] and 26% will die within 12 months of their fracture [20]. Most major osteoporotic fractures are associated with reduced relative survival, part causally related and part due to associated co-morbidity [21-23].

f. In the UK, fracture rates vary by geographic location, race and levels of socioeconomic deprivation [24-26]. As in many higher income countries, age- and sex-adjusted fracture rates appear relatively stable, although increases in hip fractures amongst men in the UK have been reported [24,27]. Changes in vertebral fracture rates potentially reflect secular alterations to reporting of cases. Importantly, ageing of the UK population is predicted to give rise to a 19.6% increase in the number of fragility fractures by 2030 if changes are not made to current practice [8].

Section 3

Fracture risk assessment and case finding

Recommendations

1. A FRAX assessment should be performed in any postmenopausal woman, or man age ≥50 years, with a clinical risk factor for fragility fracture, to guide BMD measurement and prompt timely referral and/or drug treatment, where indicated **(Strong recommendation).**
2. When using FRAX to calculate the probability of fracture, clinical judgement is needed when clinical risk exceeds those factors able to be entered into FRAX (**Strong recommendation**).
3. Arithmetic adjustments to FRAX probabilities of major osteoporotic fracture (MOF: clinical spine, hip, forearm or humerus) and hip fracture (see Table 2) can be used in clinical practice, to take account of additional clinical risk factors, such as glucocorticoid use, discordantly low lumbar spine BMD, type 2 diabetes, and a history of falls (**Conditional recommendation**).
4. Vertebral fracture assessment (VFA) is indicated in postmenopausal women, and men age ≥50 years, if there is a history of ≥4cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, a BMD T-score ≤-2.5 at either the spine or hip, or in cases of acute onset back pain with risk factors for osteoporosis **(Strong recommendation).**
5. T-scores in men and women derived from femoral neck BMD should use normative values for BMD derived from young healthy women from NHANES III **(Strong recommendation).**
6. DXA scan results should be reported within three weeks of the scan, by healthcare professionals with specific training in DXA interpretation, and in accordance with national and international reporting standards **(Strong recommendation).**
7. Patients with osteoporosis and/or a fragility fracture should be investigated for underlying causes, this includes the need for routine blood tests **(Strong recommendation).**
8. The use of quantitative ultrasound is not recommended for the diagnosis of osteoporosis **(Strong recommendation)**.
9. QCT-measured femoral neck areal BMD in postmenopausal women, and men age ≥50 years, can be used for opportunistic diagnosis of osteoporosis and to inform individual treatment decisions using FRAX **(Conditional recommendation).**
10. Computer Aided Diagnostics (CAD) may be considered to improve standard reporting of CTs performed on postmenopausal women, and men age ≥50 years, to improve opportunistic identification of vertebral fractures **(Conditional recommendation).**

Measurement of Bone Mineral Density

a. The risk of fracture increases progressively with decreasing bone mineral density (BMD). Systematic reviews and meta-analyses of observational population-based studies using absorptiometric techniques indicate that the risk of fracture increases approximately two-fold for each standard deviation (SD) decrease in BMD [28,29]; **(Evidence level Ia).** The gradient of fracture risk varies according to the site and technique used, the person's age and the fracture type [29]; **(Evidence level Ia).** The predictive value of BMD for hip fracture is at least as good as that of blood pressure for stroke [30]; **(Evidence level IV).**

b. The WHO and the International Osteoporosis Foundation (IOF) recommend that the reference technology for the measurement of BMD is dual-energy X-ray absorptiometry (DXA) applied to the femoral neck, because of its higher predictive value for fracture [31,32]; **(Evidence level Ia).** DXA measurements of femoral neck BMD are used in FRAX®. The spine is not always a reliable site for risk assessment or for the diagnosis of osteoporosis in older people because of the high prevalence of degenerative changes, which artefactually increase the BMD value. However, a result in an older person showing low BMD is almost always valid and clinically useful, particularly in those people with disproportionately low spine BMD compared to the hip.

c. At the same DXA-measured femoral neck BMD, men and women are at approximately the same fracture risk [33,34]; **(Evidence level IIa)**. Therefore, the recommended reference range, from which femoral neck and total hip T-scores are calculated for men, women and transgender individuals in the US, is that derived from the NHANES III survey for white women age 20-29 years [32,35].

d. The reference ranges, from which lumbar spine and distal forearm T-Scores are calculated, for both men and women of all ethnicities, are usually those of the manufacturer of the DXA scanner [35].

e. Osteoporosis can be diagnosed on the basis of the BMD T-score measured at the total hip, femoral neck or lumbar spine. However, fracture risk prediction is not improved by the use of measurements from multiple sites [36,37]; **(Evidence level IIa)**. Where hip BMD measurement is not possible for technical reasons, or if the spine is differentially affected, then spine BMD measurements can be used for diagnosis. A diagnosis of osteoporosis can be made based on distal forearm (1/3 radius) T-Score if neither spine nor hip can be reliably measured or interpreted, or if a patient exceeds the weight limit for the DXA table [35]; **(Evidence level IV)**.

f. Serial BMD measurement can be used to monitor response to treatment (see Section 7) [38]. Lumbar spine BMD shows the largest treatment-related changes and is the preferred site, although if spinal degenerative changes are marked,t BMD at the hip is a better site for monitoring.

g. The validity of BMD measurements depends on good quality control and national (Royal Osteoporosis Society) and international (International Society for Clinical Densitometry) bodies have published standards for the reporting of DXA scans [35,39].

h. QCT-measured femoral neck areal BMD predicts osteoporotic fractures in men and women and is equivalent to DXA-derived areal BMD [40-42]. Femoral neck and total hip T-scores calculated from two-dimensional projections of quantitative computed tomography (QCT) data are equivalent to the corresponding DXA-derived T-scores. Thus, femoral neck CT X-ray absorptiometry (CTXA) BMD measurements can be included in FRAX [35,43-45]; **(Evidence level IIa)** (see Section 4). Other techniques for assessing skeletal BMD, including quantitative ultrasound, have been less well validated than absorptiometric techniques.

Assessment of Clinical Risk Factors

i. The performance characteristics of BMD assessment can be improved by the concurrent consideration of clinical risk factors that operate independently of BMD. Of particular importance is age, which contributes to risk independently of BMD [11,46]; **(Evidence level Ia).**

j. Additional clinical risk factors have been identified that provide information on fracture risk independently of both age and BMD:

   i. Low body mass index (BMI) is a significant risk factor for hip fracture, but the value of BMI in predicting other fractures is very much diminished when adjusted for BMD [47]; **(Evidence level Ia).**

   ii. A history of a prior fracture, particularly if sustained from low-trauma and at a site characteristic for osteoporosis, is an important risk factor for further fracture [48]. The risks are in part independent of BMD [49]. Fracture risk is approximately doubled in the presence of a prior fracture, including asymptomatic moderate or severe (Grade 2 or 3) morphometric vertebral fractures [49,50]; (**Evidence level Ia**). The increase in risk is even more marked for more than one vertebral fracture. After a fracture, the risk of subsequent fracture is highest in the immediate post fracture interval (imminent risk) with more than one-third of subsequent fractures over a ten-year time frame occurring within the first year [51,52]; (**Evidence level Ic**).

   iii. A parental history of hip fracture is a significant risk factor that is largely independent of BMD [53]; (**Evidence level Ia**).

   iv. Smoking is a risk factor that is in part dependent on BMD [54]; (**Evidence level Ia**).

   v. Oral glucocorticoid therapy increases fracture risk in a dose-dependent manner. The fracture risk conferred by the use of glucocorticoids is, however, not solely dependent upon bone loss and BMD-independent risks have been identified [55,56]; (**Evidence level Ia**).

   vi. Alcohol intake shows a dose-dependent relationship with fracture risk. Where alcohol intake is on average two units or less daily, no increase in risk has been identified. Intakes of 3 or more units daily are associated with a dose-dependent increase in fracture risk [57]; (**Evidence level Ia**).

vii. There are many secondary causes of osteoporosis (e.g., inflammatory bowel disease, endocrine disorders), but in most instances it is uncertain to what extent an increase in fracture risk is dependent on low BMD or other factors such as the use of glucocorticoids. By contrast, rheumatoid arthritis increases fracture risk independently of BMD and the use of glucocorticoids [56]; (**Evidence level Ia**).

viii. Diabetes mellitus (both type 1 and type 2) is associated with an increase in risk of hip and non-vertebral fracture. In type 2 diabetes; a longer duration of disease and insulin use are associated with an increased risk [58,59]; **(Evidence level Ia),** which is partly independent of BMD [60,61].

k. The use of combined clinical risk factors alone to predict fracture risk, performs very similarly to that of BMD alone [62]. The use of clinical risk factors with the addition of BMD is optimal, but BMD measurement can be targeted to those close to the threshold of low/high risk or close to the threshold of high/very high risk (see Section 4).

l. There are many additional clinical risk factors for fracture not included in FRAX, including risks that either act solely by reducing BMD, or have been less well validated, or identify a risk that may not be amenable to particular treatments [11,63]. Liability to falls is an example of the latter where the risk of fracture is high, and treatment with drugs affecting bone metabolism alone may not fully address this risk [64].

m. In addition to glucocorticoids, several medications are known to increase hip fracture risk including thyroid hormone excess, aromatase inhibitors for the treatment of breast cancer and androgen deprivation for the treatment of prostate cancer [65-69]; **(Evidence level Ia)**. Thiazolidinediones, used in the treatment of type 2 diabetes also increase fracture risk [70,71].

n. Several other drugs have been associated with increased fracture risk including antidepressants, antiparkinsonian drugs, antipsychotic drugs, anxiolytic drugs, benzodiazepines, sedatives, H2 receptor antagonists and proton pump inhibitors [65-69]. The extent to which fracture risk is mediated by low BMD, falls risk or other factors, or indeed is definitely causal in each case, is not known. The impact of sex steroids on bone health in transgender individuals is unclear [72].

o. Biochemical indices of skeletal turnover have the potential to aid risk assessment but probably play a more immediate role in the monitoring of treatment [73-75]; **(Evidence level Ia).**

Fracture Risk Assessment Tools

p. The IOF and the WHO recommend that risk of fracture is expressed as an absolute risk, i.e., probability over a ten-year interval [11]. The absolute risk of fracture depends upon age and life expectancy as well as the current relative risk. The period of 10 years covers the likely initial duration of treatment and the benefits that may continue if treatment is stopped. Shorter time horizons do not aid the categorisation of risk [76,77].

q. Algorithms that integrate the weight of clinical risk factors for fracture risk, with or without information on BMD, were developed in 2008 by the then WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield. The FRAX tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture and/or of major osteoporotic fracture. A major osteoporotic fracture is a clinical spine, hip, forearm or humerus fracture. The tool has been externally validated in independent cohorts [46,78]; **(Evidence level Ia).**

r. QFracture is based on a UK prospective open cohort study of routinely collected data from general practices that takes into account numerous clinical risk factors and estimates the 1 to 10 year cumulative incidence of hip and/or major osteoporotic fracture [http://www.qfracture.org [79]].

s. The NICE has recommended the use of fracture risk assessment tools (FRAX or QFracture) in the assessment of patients [80]. Since FRAX and QFracture yield different outputs (probability of fracture accounting for mortality risk in the case of FRAX, and a cumulative risk of fracture in the case of QFracture), the two calculators cannot be used interchangeably. In addition, BMD cannot be incorporated into QFracture estimations. Finally, the NOGG intervention thresholds, recommended by NICE Quality Standards, are based on FRAX probability and thus cannot be used with fracture risk derived from QFracture or other calculators [78,81].

t. The input into FRAX includes, with age and sex, the BMD independent clinical risk factors listed in Table 1. Femoral neck BMD is an optional input. The listed secondary causes are conservatively assumed to be mediated through low BMD and carry no weight when femoral neck BMD is entered into FRAX.

Table 1 Clinical risk factors included specifically in the FRAX assessment of fracture probability

Age
Sex
Body mass index (calculated from weight and height in kg/m^2)
Previous fragility fracture, including morphometric vertebral fracture
Parental history of hip fracture
Current glucocorticoid treatment (any dose, by mouth for 3 months or more)
Current smoking
Alcohol intake 3 or more units daily
Rheumatoid arthritis
Secondary causes of osteoporosis including:
Type I diabetes
Long-standing untreated hyperthyroidism
Untreated hypogonadism/premature menopause (<45 years)
Chronic malnutrition/malabsorption
Chronic liver disease
Non-dialysis chronic renal failure (i.e., CKD 3a – 5)
Femoral neck BMD

N.B. Additional clinical risk factors that should prompt FRAX assessment are listed in Table 4.

u. FRAX assessment takes no account of prior osteoporosis drug treatment, or of the dose of several clinical risk factors. For example, a history of two prior fractures carries a higher risk than a single prior fracture. A prior clinical vertebral fracture carries an approximately two-fold higher risk than other prior fracture types. Dose responses are also evident for glucocorticoid use and are partially addressed in the NOGG guideline (see Section 7). Since it is not possible to model all such scenarios within the FRAX algorithm, clinical judgement is needed to interpret FRAX outputs.

v. High and low impact injuries exist on a continuum and the clinical significance of high and low impact fractures is blurred in the context of osteoporosis. Indeed, prior high-trauma fractures are associated with low BMD and future fracture risk to the same extent as fractures without high-trauma [48].

w. Although FRAX has a limited input of variables, relatively simple arithmetic procedures are available (Table 2) which can be applied to conventional FRAX estimates of probabilities of hip fracture and major osteoporotic fracture to adjust the probability assessment with knowledge of:

- High, moderate and low exposure to oral glucocorticoids [82]; **(Evidence level IIa)**
- Concurrent data on lumbar spine BMD [83,84]; **(Evidence level Ia)**
- Information on trabecular bone score (TBS) [85]; **(Evidence level Ia).** TBS values can be entered on the UK FRAX website.
- Hip axis length [86]; **(Evidence level Ib)**
- Falls history [87]; **(Evidence level IIa)**
- Country of birth [88]; **(Evidence level Ib)**
- Type II diabetes mellitus [89]; **(Evidence level Ib)**
- Recent major osteoporotic fracture (MOF) [52]; **(Evidence level Ib)**

When applying these FRAX adjustments a suggested increase of x% should be applied as a proportion of the original FRAX score. For example, uplifting the FRAX probability of 30% by 10% gives an adjusted probability of 30 x 1.10 = 33%.
There is no evidence base available to inform on the accuracy of multiple adjustments. Pragmatically, the adjustment should be made for the most dominant factor, i.e. that which will have the greater impact on the estimated probability; **(Evidence level IV).**

Table 2: Approximate adjustments and considerations to probabilities of hip fracture and major osteoporotic fracture to aid the interpretation of FRAX

Risk variable	Adjustment to FRAX*	Access
Medium and high dose exposure to oral glucocorticoids	Medium doses (2.5–7.5 mg daily) are the assumed minimum requirement for FRAX calculation, and the unadjusted FRAX value is used. For high doses (>7.5 mg daily), MOF probabilities are upward revised by about 15% and hip fracture probabilities by 20% ¥	Automatic adjustment available on FRAX website. Kanis et al 2011 [82]
Concurrent data on lumbar spine (LS) BMD	Increase/decrease MOF probability by 10% for each rounded T-score difference between LS and FN*	Leslie et al 2011 Johansson et al 2014 [83,84]
Trabecular bone score (TBS)	Increase MOF probability by 30% for each standard deviation (SD) decrease in TBS	TBS adjustment can be accessed from the UK FRAX website. McCloskey et al 2016 [85]
Hip axis length (HAL)	Increase hip fracture probability by 30% for each SD increase in HAL	Leslie et al 2016 [86]
Falls history	Increase MOF and hip fracture probability by 30% for a history of recurrent falls (≥2 falls in the last year)	Masud et al 2011 [87]
Country of birth	Use FRAX model for country of birth since individuals retain the risk characteristics of their country of origin	Johansson et al 2015 [88] Wändell et al 2021 [90]
Type II diabetes mellitus	Enter 'yes' in the rheumatoid arthritis input to FRAX	Other adjustments in Leslie et al 2018 [89]
Recent MOF	Marked uplift to fracture probabilities (see Section 4h)	Kanis et al 2020 [52]

* downward adjustment to FRAX probabilities should only be made in the context of a very reliable high lumbar spine BMD measurement and not on the basis of a discordant result due to artefact e.g. from degenerative change
¥ See Section 7: 'Glucocorticoid-induced osteoporosis' for further details on glucocorticoid doses and recommendations

x. Although type I diabetes carries a risk of fracture over and above that provided by FRAX, there are yet no empirical data from which to recommend adjustment. In the meanwhile, the same adjustment can be used as for type II diabetes; (**Evidence level IV**).

y. Additionally, FRAX values have been shown to be largely unaffected by socioeconomic status [91], variation in body composition [92], and chronic renal disease [93]; **(Evidence level Ib).**

z. Adjustments to FRAX probabilities which take into account severity and/or number of vertebral fractures cannot currently be made because of the lack of appropriate empirical data.

aa. Risk is best presented to patients numerically using simple frequencies and positive and negative framing e.g., for a 23% risk say '100 people like you, over the next 10 years, 23 will break a bone and 77 will not'. Describing risks solely with words, such as 'You have a high chance of experiencing a fracture' is ineffective and does not provide patients with the details needed to make an informed decision; it increases risk perceptions, and patients vary in their interpretations of what are low and high risks. It is easier for patients to understand whole numbers and simple frequencies (e.g., 1 in 100) rather than percentages. Graphs and pictograms make numeric information easier to understand and should be used where available [94]; (**Evidence level IV**).

Investigation of osteoporosis and fragility fractures

ab. Diagnostic assessment of individuals with osteoporosis should exclude diseases that mimic osteoporosis, identify the cause(s) of the osteoporosis, and include the management of any associated comorbidity. Common investigations are given in Table 3.

Table 3. Proposed clinical investigations to consider for the investigation of osteoporosis/ fragility fractures.

Routine	Other procedures, if indicated
• Clinical history • Physical examination including measurement of height and assessment of thoracic kyphosis • Full blood cell count • Erythrocyte sedimentation rate or C-reactive protein • Serum calcium, albumin, creatinine, phosphate[a], alkaline phosphatase[a] and liver transaminases • Serum 25-hydroxyvitamin D • Thyroid function tests	• Serum electrophoresis, serum immunoglobulins and serum free light chain assay • Plasma parathyroid hormone (PTH)[b] • Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone • 24-hour urinary free cortisol/overnight dexamethasone suppression test • Serum prolactin • Serum magnesium if hypocalcaemic • Tissue transglutaminase antibodies, +/- endomysial antibodies (coeliac disease screen) • Urinary calcium excretion • Markers of bone turnover (e.g., CTX, P1NP)[c] • Lateral radiographs of lumbar and thoracic spine or DXA based lateral vertebral imaging • Bone densitometry (DXA) if indicated by FRAX assessment and/or required for BMD monitoring • Isotope bone scan

[a] Persistent low phosphate or alkaline phosphatase should not be overlooked as this can indicate underlying metabolic bone disease.
[b] Measure PTH if albumin-adjusted serum calcium ≥2.6mmol/l twice, or if ≥2.5mmol/l twice if primary hyperparathyroidism is suspected [95].
[c] Principally measured to monitor bone turnover in response to anti-resorptive treatment (see Section 7), CTX reflects bone resorption, P1NP bone formation. CTX is best measured in the morning after an overnight fast.
Other investigations, for example, bone biopsy and genetic testing for osteogenesis imperfecta, are largely restricted to specialist centres.

Vertebral Fracture Assessment

ac. The majority of vertebral fractures do not currently come to medical attention and thus remain undiagnosed [96]. Moderate or severe vertebral fractures, even when asymptomatic, are strong risk factors for subsequent fracture at the spine and other skeletal sites [50,97,98]; **(Evidence level Ia)**. Vertebral fracture assessment (VFA) should therefore be considered in high-risk individuals, using either lateral lumbar and thoracic spine radiographs or lateral spine DXA imaging [99]; **(Evidence level Ia)**. The latter delivers a significantly lower radiation dose whilst performing comparably to traditional radiographs [100].

ad. Identification of vertebral fractures on routine radiological images, such as plain abdominal and chest radiographs, performed for other indications, offers the opportunity to detect clinically important osteoporotic fractures.

ae. Opportunistic diagnosis of osteoporosis and vertebral fractures is feasible using CT scans acquired for various clinical reasons, since the hip and spine are frequently in the scan field [101]; (**Evidence level Ia**). Vertebral fracture identification from CT using Computer Aided Diagnostics (CAD) can augment and improve standard reporting methods [102-105]; (**Evidence level IIb**)**.** Reliable CAD methods have high sensitivity, specificity, and accuracy for vertebral fracture detection; (**Evidence level IV**).

Screening and Case Finding

af. At present there is no universally accepted policy for population-based screening to identify people with osteoporosis. With the recognition that factors in addition to BMD can improve fracture risk prediction, it is possible that screening strategies might be implemented in the future.

ag. A trial of screening in the UK used FRAX to target osteoporosis drug treatment to women at high risk of hip fracture. The risk assessment, with subsequent femoral neck BMD measurement and input to FRAX in intermediate/high risk individuals, was conducted in a primary care setting and involved almost 12,500 women aged 70-85 years. Over 5 years, compared to standard clinical care, the screening program reduced the number of hip fractures by 28%. Similar results were observed in a study from Denmark [106], but with lesser effects observed in a further study in the Netherlands [107]. A meta-analysis of the three trials showed that screening reduced hip fracture risk by 20% [108]; (**Evidence level Ia**).

ah. In the absence of a screening policy, a case-finding strategy is appropriate where patients are identified because of a fragility fracture or by the presence of other clinical risk factors. There are many clinical risk factors for fracture in addition to those included in FRAX which can be used to trigger fracture risk assessment (see Table 4), including thoracic kyphosis and height loss (> 4cm), either in comparison with recalled young adult height or a documented loss on serial measurements [109]; (**Evidence level IIa**), and bariatric surgery resulting in malabsorption [110]; (**Evidence level Ia**).

Table 4. Clinical risk factors for osteoporosis/fractures, not accommodated in FRAX, which should trigger fracture risk assessment.

Thoracic kyphosis
Height loss (> 4cm)
Falls and Frailty
Inflammatory disease: e.g., ankylosing spondylitis, other inflammatory arthritides, connective tissue diseases, systemic lupus erythematosus
Endocrine disease: e.g., Type I and II diabetes mellitus [a], hyperparathyroidism, hyperthyroidism, hypogonadism, Cushing's disease/syndrome
Haematological disorders/malignancy e.g., multiple myeloma, thalassaemia
Muscle disease: e.g., myositis, myopathies and dystrophies, sarcopenia
Lung disease: e.g., asthma, cystic fibrosis, chronic obstructive pulmonary disease
HIV
Neurological/ psychiatric disease e.g., Parkinson's disease and associated syndromes, multiple sclerosis, epilepsy, stroke, depression, dementia
Nutritional deficiencies: calcium, vitamin D [note that vitamin D deficiency may contribute to fracture risk through undermineralisation of bone (osteomalacia) rather than osteoporosis]
Bariatric surgery and other conditions associated with intestinal malabsorption
Medications, e.g.:
Some immunosuppressants (calmodulin/calcineurine phosphatase inhibitors)
(Excess) thyroid hormone treatment (levothyroxine and/or liothyronine). Patients with thyroid cancer with suppressed TSH are at particular risk
Drugs affecting gonadal hormone production (aromatase inhibitors, androgen deprivation therapy, medroxyprogesterone acetate, gonadotrophin hormone releasing agonists, gonadotrophin hormone receptor antagonists)
Some diabetes drugs (e.g., thiazolidinediones)
Some antiepileptics (e.g., phenytoin and carbamazepine)

[a] Able to be accommodated in FRAX by proxy, by entering 'yes' in the rheumatoid arthritis input (see Table 2)

Section 4

Intervention thresholds and strategy

Recommendations

1. An initial FRAX assessment, which provides the ten-year probability of a major osteoporotic fracture (MOF; clinical spine, hip, forearm or humerus) and/or hip fracture, can be used to identify patients at low, intermediate, high or very high risk of fracture **(Strong recommendation).**
2. Consider, particularly in older people, drug treatment in those with a prior and/or recent fragility fracture, with fracture risk assessment informing the choice of drug treatment **(Strong recommendation).**
3. Men and women with high and very high fracture risk (see Figure 1) should have a DXA if a baseline measurement is needed against which to compare future BMD measurements **(Strong recommendation).**
4. Men and women with intermediate fracture risk (i.e., between the upper and lower assessment thresholds) should be referred for BMD measurement, if practical. Thereafter, fracture probability should be reassessed using FRAX **(Strong recommendation)**.
5. When BMD is included in a FRAX assessment, the patient's risk (high, very high or low) is determined by the higher of the two (MOF and hip fracture) risk assessments **(Strong recommendation)**.
6. In men and women with intermediate fracture risk, if BMD measurement is unavailable, contraindicated, or impractical (e.g., in frail individuals), drug treatment should be offered if there is a history of fragility fracture and/or if fracture risk exceeds the intervention threshold **(Strong recommendation)**.
7. Men and women with low fracture risk, without a prior fragility fracture, can be reassured that their fracture risk is low and offered lifestyle advice as appropriate **(Strong recommendation)**.
8. Consider referral of very high-risk patients to an osteoporosis specialist in secondary care, for assessment and consideration of parenteral treatment (some may need first-line anabolic drug treatment, especially those with multiple vertebral fractures). Indications for specialist referral include **(Conditional recommendation)**:
    - The presence of single but important clinical risk factors, such as,
        - A recent vertebral fracture [within the last 2 years]
        - ≥2 vertebral fractures [whenever they have occurred]
        - BMD T-Score ≤-3.5
        - Treatment with high dose glucocorticoids [≥7.5 mg/day of prednisolone or equivalent over 3 months] (refer urgently given rapid loss in bone post initiation of glucocorticoids; if any delay is anticipated, start an oral bisphosphonate in the meantime)
    - The presence of multiple clinical risk factors, particularly with a recent fragility fracture indicating high imminent risk of re-fracture,
    - Or other indicators of very high fracture risk.
9. The choice of drug treatment should be informed by the level of fracture risk, additional clinical risk factors, cost-effectiveness of treatment and patient preferences **(Strong recommendation)**.
10. FRAX and the link to the NOGG website should be incorporated into electronic patient health record systems (**Strong recommendation**).

FRAX assessment thresholds for ten-year probability of fracture

a. The approach recommended for decision-making is based on fracture probabilities derived from FRAX and can be applied to men and women [78]. This approach is underpinned by cost-effectiveness analysis with oral or intravenous bisphosphonates as the intervention [111,112]; **(Evidence level Ib).** FRAX assessment thresholds for ten-year probability of a major osteoporotic fracture (MOF) are shown in Figure 1.

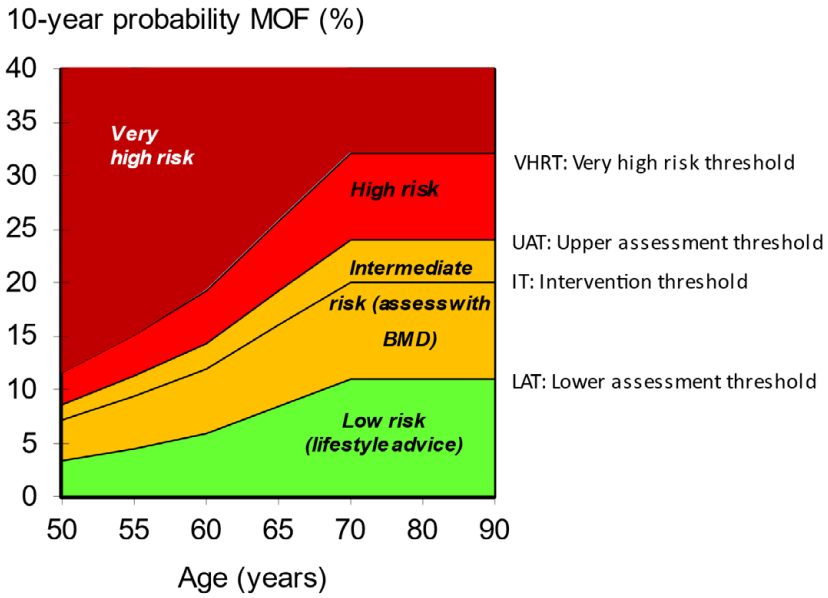


Figure 1: NOGG assessment, intervention and risk thresholds for major osteoporotic fracture probability (MOF) in the UK with the use of FRAX. Individuals with probabilities below the lower assessment threshold (LAT) are considered for lifestyle advice. Those at intermediate risk (probabilities between the upper assessment threshold (UAT) and lower assessment threshold (LAT) are further assessed with BMD measurement. Where probabilities calculated using BMD lie above or below the intervention threshold (IT), treatment or lifestyle advice, respectively, is recommended [3,78]. Patients with probabilities above the upper assessment threshold (UAT) are considered for treatment. Those with probabilities above the very high-risk threshold (VHRT) should be considered for specialist referral. Where BMD measurement is not practical (e.g. when individuals are frail and unable to get onto a DXA table, or lie flat on a DXA table), patients with probabilities above the IT are considered for treatment.

b. The use of FRAX without BMD has approximately the same performance as BMD without FRAX [11]; **(Evidence level Ia).** Thus, the same intervention threshold can be used when fracture risk is assessed with or without BMD (see Figure 1).

c. For men and women, the intervention threshold up to age 70 years is set at a risk equivalent to that of a woman of the same age with a prior fracture, in line with current clinical practice, and therefore rises with age. At age 70 years and above, fixed thresholds are applied [113]; **(Evidence level Ib).** The proportion of women potentially eligible for treatment rises from approximately 30% to 50% with age, largely driven by the prevalence of prior fracture [113]; **(Evidence level Ib).**

d. When FRAX is calculated with BMD included, the NOGG website also provides intervention thresholds based on the 10-year probability of hip fracture, in addition to the 10-year probability of a MOF (Figure 2). If there is discordance between the risk categories identified by the two probabilities, the highest risk category can be used to guide intervention. Of note, in the SCOOP study of screening for high fracture risk, treatment was targeted on the basis of risk assessed by hip fracture probability, with or without BMD [114].

Indications for specialist referral in those at very high fracture risk

e. Individuals at very high fracture risk have the most to gain from thorough investigation of osteoporosis, falls assessment, and development and delivery of a personalised treatment plan for a chronic, life-long condition. A number of treatments now available to treat osteoporosis are mostly (but not exclusively) initiated through secondary care (see Section 6), and the sequence in which they are used is important; for example, the two available anabolic agents (teriparatide and romosozumab) are licensed for once only treatment courses (see Section 6).

f. Treatment with teriparatide or romosozumab, which are anabolic skeletal agents, result in rapid and greater fracture risk reductions than some antiresorptive treatments (see Section 6) [115-117]; **(Evidence level Ib).** This has led to the need to identify the sub-group of patients at very high fracture risk who would potentially benefit from clinical review by an osteoporosis specialist, and who may benefit from anabolic drug treatment [118].

g. Indications for referral to an osteoporosis specialist may arise through several routes, for example in the presence of single but important clinical risk factors, such as a recent vertebral fracture [within the last 2 years], ≥2 vertebral fractures [whenever they have occurred], a BMD T-Score ≤-3.5, high dose glucocorticoids use (≥7.5 mg/day of prednisolone or equivalent over 3 months) (see Section 7) [55,119]; **(Evidence levels IIb and IV)**, or via a combination of clinical risk factors, resulting in very high fracture risk [120]; **(Evidence level IIb).**

h. Prior fragility fracture is a well-established risk factor for a future fracture. This risk of subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively over the next 2 years, but thereafter remains higher than that of the general population [98,121-128]. This effect of recency of fracture, sometimes termed imminent risk [127], is also dependent on age, sex and site of fracture [52] ; **(Evidence level Ic)**. This complexity is being addressed by the development of optional post-FRAX algorithms to allow clinicians to explore the potential impact of fracture recency on the calculated probability of MOF and hip fracture (see Table 2) [52]. The mechanism underlying imminent risk is not yet fully understood and no clinical risk factors have yet been identified for short term recurrent fractures that differ from those identified for fracture over a longer time horizon [77]. Few therapeutic studies have reported the recency of fracture in those patients whom they have recruited, though rapid clinical efficacy has been demonstrated within studies of zoledronate, risedronate, teriparatide and romozozumab [116,129,130]; **(Evidence level Ib).**

i. A NOGG threshold that characterises men and women at high and very high fracture risk has also been established using FRAX probabilities; very high risk is identified as a FRAX-based fracture probability that exceeds the intervention threshold by 60% (Figures 1 and 2) [131]. It can be used to identify patients who likely require specialist referral for assessment of their osteoporosis (which should include DXA measurement of BMD), and further consideration of appropriate treatment strategies [118,132]. The proportion of postmenopausal women at very high risk defined in this way rises from approximately 6% at age 50-54 to 36% at age 90 years or older. Numerical values for the probability thresholds are given in Table 5 for MOF and for hip fracture. An assessment algorithm is shown in Figure 3.

j. In patients with FRAX probabilities in the high-risk category, consideration of additional clinical risk factors (e.g., frequent falls, very low spine BMD – see Table 2) can also lead to redesignation from high to very high risk of fracture.

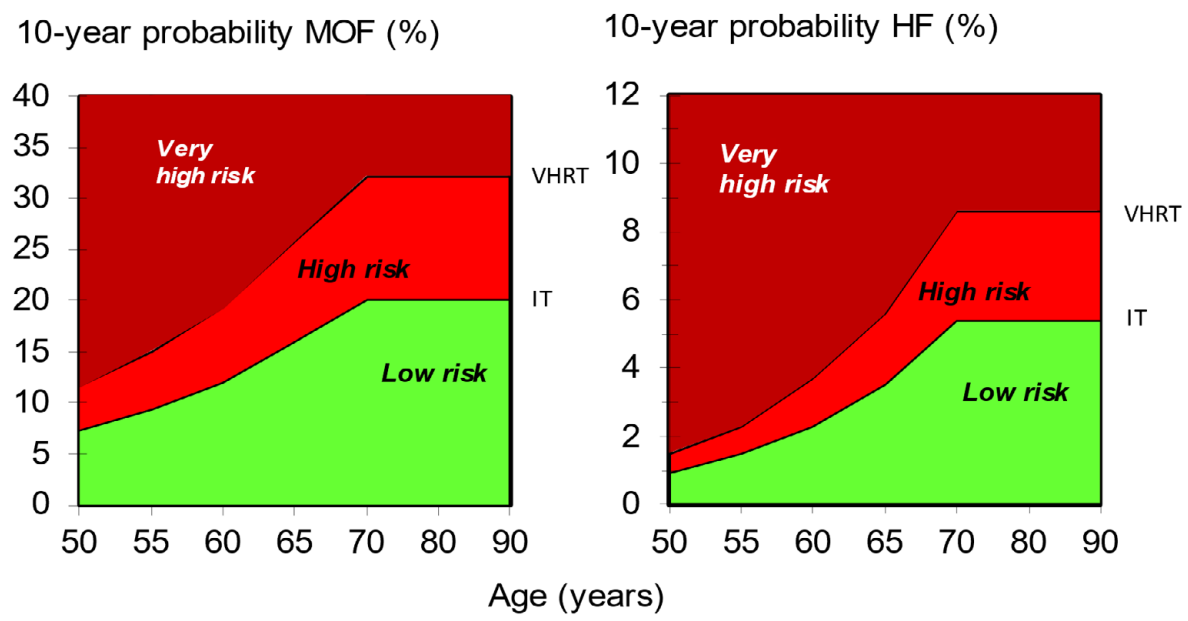


Figure 2: NOGG thresholds for intervention and/or referral using major osteoporotic fracture (MOF) and hip fracture (HF) probabilities in the UK. The panels show the thresholds following the recalculation of FRAX after the input of BMD; the same thresholds are used when BMD is unavailable. The intervention threshold (IT) and very high-risk threshold (VHRT) denote the thresholds for high and very high risk, respectively.

Table 5 Numerical values for NOGG thresholds for major osteoporotic fracture and hip fracture probabilities based on FRAX. LAT and UAT refer to the lower and upper assessment thresholds, respectively, between which a BMD is indicated. The intervention threshold (IT) and very high-risk threshold (VHRT) denote the thresholds for high and very high risk.

Age (years)	LAT	IT	UAT	VHRT
Major osteoporotic fracture				
50	3.4	7.3	8.8	11.7
55	4.5	9.5	11.4	15.2
60	6.0	12.2	14.6	19.4
65	8.6	16.5	19.8	26.4
70	11.1	20.3	24.4	32.5
Hip fracture				
50	0.23	0.91	1.1	1.5
55	0.43	1.5	1.7	2.3
60	0.80	2.3	2.8	3.7
65	1.4	3.5	4.2	5.6
70	2.6	5.4	6.5	8.6

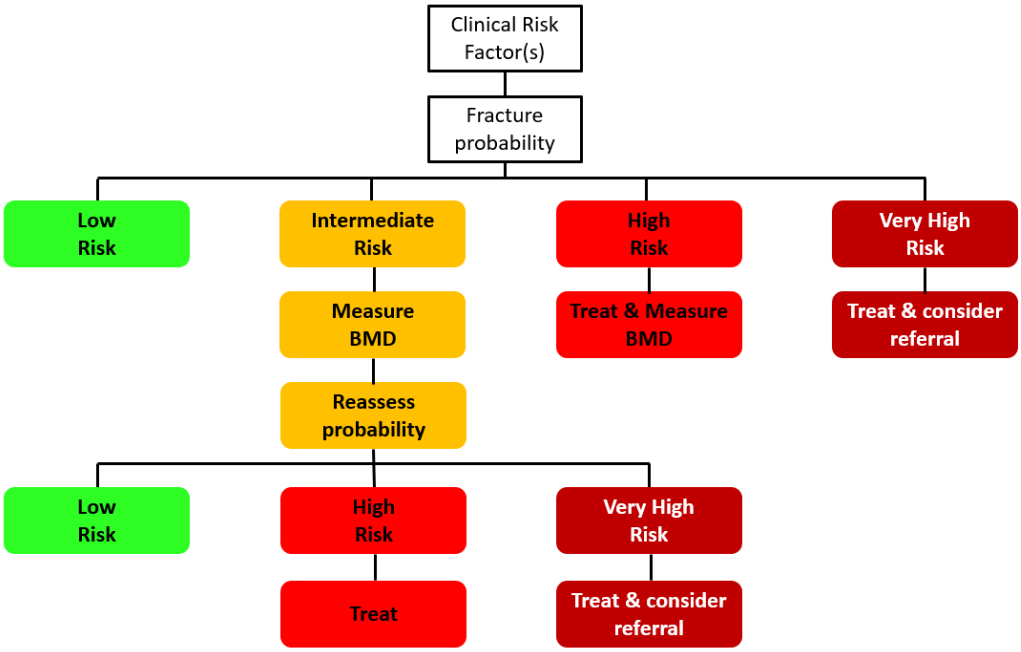


Figure 3: Management algorithm for the assessment of individuals at risk of fracture [131]. Those at very high risk should be treated and considered for referral to an osteoporosis specialist in secondary care; some may benefit from parenteral treatment (including first-line anabolic drug treatment, especially if multiple vertebral fractures). All individuals should be offered lifestyle advice. CRF: Clinical Risk Factor.

FRAX – Practical considerations

k. The FRAX MOF probabilities are transferred automatically to the NOGG website, by clicking on the specified button on the FRAX results box. Where practitioners receive the results of a FRAX risk assessment for an individual patient without treatment guidance, the FRAX probabilities can also be entered manually onto the NOGG website (www.nogg.org.uk/manual-data-entry); this page also captures additional information (age, sex, glucocorticoid exposure and finally, whether a femoral neck BMD has been included, in the FRAX estimates) so that the result can be automatically compared to the NOGG thresholds with appropriate guidance on treatment.

l. Lack of integration of FRAX assessments and links to NOGG guidance in existing patient health record systems represents a barrier to effective fracture risk assessment **(Evidence IV).**

m. The targeted use of BMD assessments with the NOGG strategy makes more efficient use of often limited resources than would DXA scanning of all individuals with risk factors [133]; **(Evidence level Ib).** Historically it was thought that treatment should not be undertaken in women without initial BMD measurement, except in those with hip or vertebral fractures. This view arose after a post-hoc analysis in 1998 suggested reduced efficacy of alendronate in patients with BMD T-scores above -2.5 [134]; **(Evidence level Ib).** However, this approach is now outdated as many studies have since shown little or no interaction of BMD on the effectiveness of several agents, including bisphosphonates (e.g., zoledronate, denosumab, raloxifene, and teriparatide) [63,135-138]; **(Evidence level Ib).** Moreover, clinical risk factors are not independent of BMD and, when clinical risk factors alone are used in women age 70 years or more to identify patients at high fracture risk, BMD is approximately 1SD lower in the high-risk group compared with a low-risk group [139,140]; **(Evidence level Ib).** These findings indicate that the categorisation of patients at high fracture risk on the basis of FRAX without BMD mostly selects patients with low BMD and that the higher the fracture probability, the lower the BMD. Note that this does not preclude the use of DXA scanning if more widely available; in addition to providing the most accurate risk assessment, DXA provides a baseline measurement for treatment monitoring and also permits, again if available and indicated, detection of vertebral fractures using VFA (see Section 3).

n. FRAX is not recommended as a tool to monitor treatment [141]; **(Evidence level IIb)**. However, the use of FRAX is appropriate to re-evaluate current fracture probabilities when considering a change in patient management; **(Evidence level IV)**.

Section 5

Non-pharmacological management of osteoporosis

Recommendations

Postmenopausal women, and men age ≥50 years, with osteoporosis or who are at risk of fragility fracture are recommended:

1. A healthy, nutrient-rich balanced diet **(Strong recommendation).**
2. An adequate intake of calcium (minimum 700mg daily) preferably achieved through dietary intake or otherwise by supplementation **(Strong recommendation).**
3. To consume vitamin D from foods be prescribed vitamin D supplements of at least 800IU/day if they have identified vitamin D insufficiency or risk factors for vitamin D insufficiency. Those who are either housebound or living in residential or nursing care are more likely to require calcium and vitamin D supplementation to achieve recommended levels of intake **(Strong recommendation).**
4. A combination of regular weight-bearing and muscle strengthening exercise, tailored according to the individual patient's needs and ability **(Strong recommendation).**
5. Advice about smoking cessation if an individual is a smoker **(Strong recommendation).**
6. Advice to restrict alcohol intake to ≤ 2 units/day **(Strong recommendation).**
7. A falls assessment should be undertaken in all patients with osteoporosis and fragility fractures; those at risk should be offered exercise programmes to improve balance and/or that contain a combined exercise protocol **(Strong recommendation)**.

Dietary modification

a. A meta-analysis of observational studies examining different dietary patterns found a modest reduction in risk of low BMD and of hip fractures in subjects adhering to 'healthy' (high in fruit and vegetables, fish, poultry and whole grains) diets and a reduction in risk of low BMD in those with 'milk/dairy' diets. By contrast, those with a 'meat/Western' dietary pattern (high in processed and red meat, animal fat, refined sugar and soft drinks) saw a modest increase in risk of low BMD and of hip fractures. However, population heterogeneity with inclusion of subjects aged under 25 years in many dietary studies reduces generalisability [142]; **(Evidence level IIa).** A randomised controlled trial of a 'healthy diet' consumed for 30 days, specifically a calcium-rich diet that emphasizes fruits, vegetables and low-fat dairy products (Dietary Approaches to Stop Hypertension (DASH)), resulted in reduction in bone turnover [143]; **(Evidence level Ib).**

b. Protein is an important constituent of bone and muscle tissue, and good dietary intake is necessary to maintain the health of the musculoskeletal system. Protein intakes higher than the recommended daily allowance (RDA) of 0.75g/kg body weight/day are associated with higher BMD at the neck of femur and total hip in one RCT, and in observational studies, has been associated with a reduced risk of hip fractures[144,145]; **(Evidence levels Ib and IIa)**; however, in a meta-analysis of 30 interventional studies, no significant effects of protein supplementation on BMD were seen[145]; **(Evidence level Ia)**. Post-operative protein supplementation in patients with a recent hip fracture has been shown to improve the subsequent clinical course by significantly lowering rates of infection and duration of hospital stay [146]; **(Evidence level Ib).**

c. Whilst there are inconsistencies in the evidence base for the associations between vegetarian and vegan diets and musculoskeletal health, consumption of a vegetarian or vegan diet has been associated with lower BMD at the lumbar spine and hip than an omnivore diet, and a vegan diet has been associated with higher fracture risk [147]; **(Evidence level IIa).** A subsequent prospective cohort study of 65,000 people in the UK also identified lower BMD at the spine and hip in vegans and vegetarians, and higher hip fracture risk in vegans, attenuated in part by adjustment for calcium and/or protein intake [148]; **(Evidence level IIb).**

Calcium and vitamin D

d. At every stage of life, adequate dietary intakes of key bone nutrients such as calcium and vitamin D contribute to bone health. The UK Reference Nutrient Intake per day of calcium is 700mg for adults aged 19 years and older [149]. Dietary calcium calculators are available to assess intake e.g., https://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator/. Whilst the Scientific Advisory Committee on Nutrition (SACN) recommends a reference nutrient intake (RNI) of 400 IU daily of vitamin D for adults of all ages [150], in the context of osteoporosis higher levels, specifically 800 up to 2,000 IU daily may be appropriate [151]; **(Evidence level IV)**.

e. Most randomised controlled trials of anti-resorptive and anabolic drugs (see Section 6) have included co-administration of calcium and vitamin D supplements. There have been many randomised controlled trials of either calcium alone, vitamin D alone or both in combination to examine whether use of these supplements alone reduces fracture risk. With respect to combined calcium and vitamin D supplements, meta-analyses have reported reduction in hip and non-vertebral fractures, and possibly also in vertebral fractures [152-154]; **(Evidence level Ia)**. Overall, there is little evidence that vitamin D supplementation alone reduces fracture incidence, although it may reduce falls risk [154,155]; **(Evidence level Ib).** However, it is important for patients taking antiresorptive and anabolic osteoporosis drug therapies to be vitamin D replete. In clinical practice, dietary sources of calcium are the preferred option and calcium (combined with vitamin D) supplementation should be targeted to those who do not get sufficient calcium from their diet and who are at risk of osteoporosis and/or fragility fracture, such as older adults who are housebound or living in residential or nursing care [153], and those with intestinal malabsorption e.g. due to chronic inflammatory bowel disease, or following bariatric surgery. Calcium and vitamin D supplements may increase the risk of kidney stones, but not the incidence of cardiovascular disease or cancer [156]; **(Evidence level Ia).** Routine intermittent administration of large doses of vitamin D e.g. ≥60,000 IU is not advised, based on reports of an associated increased risk of fracture and falls [157,158]; **(Evidence level Ia)**.

Exercise to improve or maintain bone density

f. Exercise has beneficial effects on BMD [159] **(Evidence level Ia)**; however, clear evidence for a reduction in fracture risk is wanting. The effect of exercise on different skeletal sites varies. Combination exercise programmes, which include weight-bearing and resistance strengthening exercise, are effective at reducing bone loss in the femoral neck and lumbar spine in post-menopausal women [159,160]; **(Evidence level Ia)**. Similarly, upper body resistance exercise increases forearm bone mass [161]; **(Evidence level Ia)**. A meta-analysis of the effects of exercise interventions on BMD in men found only three studies and identified a significant but moderate improvement in BMD at the femoral neck and a trend towards increased BMD at the lumbar spine [162]; **(Evidence level Ia)**.

g. The effect of exercise varies with intensity and duration. Strengthening (resistance) exercise may be more effective if supervised. People at risk of falls, or with vertebral fractures, may need more specific advice and assessment before increasing exercise intensity [163] (see Section 8). The NOGG supports the Royal Osteoporosis Society Strong, Steady and Straight Expert Consensus Statement, which offers advice on intensity and duration and linked patient information videos and factsheets [163].

h. In people with osteoporosis, repetitive forced spinal forward flexion exercises should be undertaken with care as this specific movement may be associated with an increased risk of new vertebral fractures [164]; **(Evidence level Ia)**. However, in general people with osteoporosis can safely participate in exercise because the risk of serious adverse events is very low [164]; **(Evidence level Ia)**.

Falls interventions

k. The majority of non-vertebral fractures are preceded by a fall. Exercise can significantly reduce the risk of falls and, perhaps the risk of subsequent fractures, by maintaining or restoring muscle strength, balance and posture, improving confidence and reaction times. However, two recent large randomised controlled trials have not demonstrated an effect of multi-disciplinary interventions, targeted at falls, on fracture reduction, when combined with screening for falls risk in primary care [165,166]; **(Evidence level Ib)**, a recent Cochrane review of falls prevention exercise programmes, and two previous meta-analysis demonstrated, albeit with low certainty, evidence of a reduction in fall-related fractures (or falls resulting in fractures) in those living in the community [160,167,168]; **(Evidence level Ia)**.

l. Exercise interventions to reduce falls in people with osteoporosis and/or at high risk of falling, have been found to be safe [169]; **(Evidence level Ia)**.

m. Programmes that involve balance training and/or a combined exercise protocol are more effective in those who have risk factors for falling [167,169]; **(Evidence level Ia)**. Combined exercise protocols may include resistance training, balance challenging, aerobic exercise and impact exercise. Interventions of 3 hours per week or more are most effective [170]; **(Evidence level Ia)**. Interventions of short duration (less than 6 months) have found to be effective, and good compliance with exercise interventions has been reported [169]; **(Evidence level Ia).**

n. Home safety interventions (best delivered by an occupational therapist) have been shown to reduce the risk of falls in people living in the community [171]; **(Evidence level Ia).** Furthermore, whole body vibration has been demonstrated to reduce fall rate but does not increase BMD [172]; **(Evidence level Ia).**

Lifestyle measures

o. Other measures to improve bone health include optimisation of body mass index if under or overweight, stopping smoking and reducing alcohol intake. Smoking cessation has been demonstrated to reduce the risk of vertebral and hip fractures in women [173,174]; **(Evidence levels IIb and IIa)**. However, risk of hip fracture was reduced in those who had stopped smoking, compared with current smokers, only after 5 years. Furthermore, pre-operative smoking cessation is associated with fewer post-operative complications [175]; **(Evidence level Ia)**. In men with previous alcohol dependence, BMD is significantly lower than controls, but improves following 3-4 years of abstinence [176]; **(Evidence level IIa)**. National guidelines recommend alcohol intake is limited to ≤ 2 units/day for women and men [177].

Section 6

Pharmacological treatment options

Recommendations

1. Fracture risk assessment, patient suitability and preference and cost-effectiveness should inform the choice of drug treatment. In most people at risk of fragility fracture, anti-resorptive therapy is the first-line option (**Strong recommendation**).

Antiresorptive drug treatment

2. Offer oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate as the most cost-effective interventions. Alternative options include denosumab, ibandronate, hormone replacement therapy, raloxifene and strontium ranelate (**Strong Recommendation**).
3. Offer intravenous zoledronate as a first-line treatment option following a hip fracture (**Strong Recommendation**).
4. Before starting denosumab, ensure a long-term personalised osteoporosis management plan is in place and that both the patient and the primary care practitioner are made aware that denosumab treatment should not be stopped or delayed without discussion with a healthcare professional (**Strong recommendation**).
5. Avoid unplanned cessation of denosumab because it can lead to increased vertebral fracture risk, hence it must not be stopped without considering an alternative therapy (**Strong recommendation**).
6. If denosumab therapy is stopped, intravenous infusion of zoledronate is recommended 6 months after the last injection of denosumab, with subsequent monitoring of serum CTX guiding the timing of further treatment (**Strong Recommendation**). Where monitoring of serum CTX is not possible, consider a further intravenous infusion of zoledronate 6 months after the first dose of zoledronate (**Conditional Recommendation**).
7. Limit the initiation of HRT for the treatment of postmenopausal osteoporosis to younger post-menopausal women (age ≤ 60 years) who have low baseline risk for adverse malignant and thromboembolic events (**Strong recommendation**).
8. Discuss continued use of HRT after the age of 60 years with the patient, with treatment based on an individual risk-benefit analysis (**Conditional recommendation**).

Anabolic drug treatment

9. Consider teriparatide or romosozumab as first-line treatment options in postmenopausal women at very high fracture risk, particularly in those with vertebral fractures (see Section 4) (**Conditional Recommendation**).
10. Consider teriparatide as a first-line treatment option in men age 50 years and older who are at very high fracture risk, particularly in those with vertebral fractures (see Section 4) (**Conditional Recommendation**).
11. Consider as second-line treatment options, teriparatide in postmenopausal women, and men age 50 years and older, and romosozumab in postmenopausal women, who are intolerant of bisphosphonate treatment, particularly in those with vertebral fractures (**Conditional recommendation**).
12. Following the approved duration of treatment with teriparatide or romosozumab (24 or 12 months respectively), initiate treatment with alendronate, zoledronate or denosumab without delay (**Strong Recommendation**).
13. Consider raloxifene as an option for follow-on treatment after an anabolic drug in women (**Conditional recommendation**).

Other treatments

14. When other antiresorptive and anabolic treatments are contraindicated or not tolerated, strontium ranelate can be used to treat postmenopausal osteoporosis and men with severe osteoporosis, provided the risk-benefit in relation to cardiovascular and thromboembolic events is considered. Initiation by a specialist who is an expert in osteoporosis management is advised (**Strong recommendation**).

15. Offer calcium and/or vitamin D supplementation as an adjunct to anti-osteoporosis drug treatment, if dietary calcium is low and/or vitamin D insufficiency is a risk, respectively (**Strong recommendation**).
16. Treat vitamin D deficiency and insufficiency prior to initiation of parenteral anti-osteoporosis drug treatment, and alongside initiation of oral anti-osteoporosis drug treatment (**Strong recommendation**).

Overview of treatment options

Drugs used in the management of osteoporosis can be considered under two broad headings based on their primary mode of action. **Anti-resorptive drugs** primarily inhibit osteoclastic bone resorption with later secondary effects on bone formation. **Anabolic drugs** primarily stimulate osteoblastic bone formation with variable effects on bone resorption. Most drugs fit into one or other category but romosozumab has a dual action, both stimulating bone formation and inhibiting bone resorption. Anti-resorptive drugs are much less expensive than anabolic drugs. It is important to consider the long-term management strategy for each patient initiated on osteoporosis treatment, as the timing of use of certain drugs is important, for example teriparatide can only be used once in a lifetime, whilst denosumab requires careful consideration before initiation given the difficulties in stopping treatment once it is started.
The drugs listed in table 6 have been shown to reduce fragility fractures in postmenopausal women, and men where indicated, with osteoporosis [178] **(Evidence levels Ia and Ib).**

Table 6. Anti-fracture efficacy of approved drug treatments for postmenopausal women, and men, with osteoporosis when given with calcium and vitamin D

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

Evidence levels shown (see Appendix 3). HRT: hormone replacement therapy. NAE: No available evidence.

a. Vertebral Fractures

The efficacy of the drugs listed in Table 6 is well established for the prevention of vertebral fractures. Teriparatide and romosozumab are superior to risedronate and alendronate respectively at reducing vertebral fractures in high-risk postmenopausal women with osteoporosis.

b. Hip fractures

Most drugs listed in Table 6 have been shown to reduce hip fracture incidence, with the exception of ibandronate, calcitriol and raloxifene.

c. Non-vertebral fractures

Drugs listed in Table 6 (except calcitriol and raloxifene) have been shown to reduce the incidence of non-vertebral fractures.

d. Drug initiation

Primary and secondary care initiation

Oral and intravenous bisphosphonates, denosumab, raloxifene, calcitriol, and HRT can be initiated by primary or secondary care clinicians. If denosumab is initiated in primary care, consultation with secondary care colleagues is advised given the need to have a long-term personalised osteoporosis management plan in place before denosumab is started, to enable denosumab, to be stopped in a managed way, as necessary.

As calcitriol use is only supported by a grade IIa evidence base, its use is generally restricted to a select sub-group managed through secondary care. Strontium ranelate can be initiated by primary or secondary care clinicians, but if started in primary care should involve consultation with secondary care.

Secondary care initiation

Teriparatide and romosozumab should be initiated by secondary care clinicians. In the UK both are provided via 'home healthcare' services, which also provide patient education.

e. Treatment sequence

Any patient stopping denosumab, romosozumab or teriparatide requires a sequential therapy strategy usually involving an anti-resorptive drug, which should be planned at the time the initial therapy is instigated to avoid a gap in treatment.

Specific drug options

Anti-resorptive drugs: Bisphosphonates

Alendronate 70mg once weekly by mouth is recommended for the treatment of women with postmenopausal osteoporosis (PMO), men with osteoporosis; glucocorticoid induced osteoporosis (GIO) and the prevention of PMO and GIO.

a. The 70mg weekly dose is considered equivalent to the previously approved dose of 10mg daily.

b. In postmenopausal women with osteoporosis, alendronate has been shown to reduce vertebral, non-vertebral and hip fractures [179]; **(Evidence level Ib).** Approval for the use of alendronate in men with osteoporosis and in men and women taking glucocorticoids was granted on the basis of BMD bridging studies [180,181]; **(Evidence level Ib).** Although the daily dose of alendronate (10mgs) is licenced for use in men, this is considered equivalent to the weekly dose (70mg); **(Evidence level IV).**

c. Common side-effects of alendronate include upper gastrointestinal symptoms, bowel disturbance, headaches and musculoskeletal pain.

d. Alendronate should be 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 medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (~200ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 30 minutes after taking the tablet. Alendronate is also available as 70mg effervescent or soluble tablets, to be dissolved in a glass of plain water (^{3}120ml).

Risedronate 35 mg once weekly by mouth is recommended for the treatment of PMO, men with osteoporosis; GIO and the prevention of GIO in women.

a. The 35mg weekly dose is considered equivalent to the previously approved dose of 5mg daily.

b. In postmenopausal women with osteoporosis, risedronate has been shown to reduce vertebral and non-vertebral fractures [182,183]; **(Evidence level Ib**). In a large population of older women, risedronate significantly decreased the risk of hip fractures, an effect that was greater in osteoporotic women [64]; **(Evidence level Ib).** Approval for use of risedronate in men with osteoporosis and in postmenopausal women taking glucocorticoids was granted on the basis of BMD bridging studies [184-186]; **(Evidence levels Ib).**

c. Common side-effects include upper gastrointestinal symptoms, bowel disturbance, headache and musculoskeletal pain.

e. Risedronate should be 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 medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (^{3}120ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 30 minutes after taking the tablet.

Ibandronate 150mg once monthly by mouth or 3mg as a prefilled intravenous injection (usually given as a 15-30 second push via butterfly cannula) every 3 months is recommended for the treatment of postmenopausal women with osteoporosis.

a. The 150mg monthly dose and 3mg 3-monthly intravenous dose are considered equivalent to the following doses: 2.5mg daily by mouth for the treatment of PMO.

b. In postmenopausal women with osteoporosis, ibandronate 2.5mg daily has been shown to reduce vertebral fracture incidence [187]; **(Evidence level Ib).** In a post-hoc analysis of women at high fracture risk (with a femoral neck BMD T-score below -3.0), a significant reduction in non-vertebral fractures was shown [188]; **(Evidence level Ib).** No data are available to show efficacy of hip fracture risk reduction. Approval for the oral 150mg once monthly and 3mg intravenously every 3 months formulations was granted on the basis of BMD bridging studies [189,190]; **(Evidence levels Ib).**

c. Common side-effects with the oral preparation include upper gastrointestinal side-effects and bowel disturbance. Intravenous administration may be associated with an acute phase reaction, characterised by an influenza-like illness; this is generally short-lived and typically occurs only after the first injection.

d. Oral ibandronate should be taken after an overnight fast and 1 hour before the first food or drink (other than water) of the day, or any other oral medicinal products or supplementation (including calcium). Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking the tablet.

Zoledronate 5mg once yearly by intravenous infusion (as 5mg/100ml infusion given over a minimum of 15 minutes via an intravenous cannula) is recommended for the treatment of PMO, men with osteoporosis and men and postmenopausal women with GIO.

a. In postmenopausal women with osteoporosis, zoledronate 5mg once yearly has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures [191]; **(Evidence level Ib).** Approval for use of zoledronate in men with osteoporosis and in men and women taking glucocorticoids was granted on the basis of BMD bridging studies [192,193]; **(Evidence levels Ib).**

b. When given shortly after hip fracture, men and women given zoledronate 5mg annually had had fewer clinical fractures and lower mortality 3 years later [130]; **(Evidence level Ib).**

c. When given (without calcium supplementation) every 18 months to women with osteopenia, there were fewer vertebral and non-vertebral fractures [138,194]; **(Evidence level Ib).** A lower although non-significant decrease in mortality in fracture-free women, fewer breast cancers and fewer non-breast cancers were also reported as secondary outcomes by the end of the 6-year study.

d. Common side-effects include an acute phase reaction usually only after the first infusion [195], which can be ameliorated by co-administration of paracetamol. Glomerular filtration rate (eGFR) should be calculated prior to initiation of treatment and caution advised for recipients at risk of kidney failure; monitoring for any increase in serum creatinine or reduction in eGFR. The MHRA recommends use of creatinine clearance instead of eGFR to inform treatment decisions in those age over 75 years and/or with BMI <18 or >40 kg/m^2. An increase in symptomatic atrial fibrillation, reported as a serious adverse event, was seen in the main phase III trial [191]; **(Evidence level Ib).**

Contraindications and special precautions for the use of bisphosphonates

a. Oral and intravenous bisphosphonates are contraindicated in patients with hypocalcaemia, hypersensitivity to bisphosphonates, in women who are pregnant or lactating. Oral bisphosphonates are contraindicated in people with abnormalities of the oesophagus that delay oesophageal emptying such as stricture or achalasia, and inability to stand or sit upright for at least 30-60 minutes. They should be used with caution in patients with other upper gastrointestinal disorders.

b. Zoledronate and risedronate are contraindicated in severe renal impairment (GFR ≤ 35 ml/min for zoledronate and ≤30 ml/min for risedronate), whilst alendronate and ibandronate are cautioned against (GFR ≤35 ml/min for alendronate and ≤ 30 ml/min for ibandronate).

c. Pre-existing hypocalcaemia must be investigated and, where due to vitamin D deficiency, treated with vitamin D (e.g., 100,000 to 300,000 IU orally as a loading dose in divided doses) before zoledronate treatment is initiated.

d. Rare adverse effects of long-term bisphosphonate treatment including osteonecrosis of the jaw and atypical femoral fractures are addressed in Section 7.

Anti-resorptive drugs: Denosumab

Denosumab is a fully humanised monoclonal antibody against Receptor Activator of Nuclear factor Kappa B Ligand (RANKL), a major regulator of osteoclast development and activity. It is approved for the treatment of PMO and men at increased fracture risk, for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased fracture risk (see Section 7), and for the treatment of bone loss associated with long term systemic glucocorticoid therapy in adults at risk of fragility fracture (see Section 7) [196]; **(Evidence level Ib).**

Denosumab is given as a subcutaneous injection of 60 mg once every 6 months. It has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis [197] and safety and efficacy are maintained over 10 years of treatment [198]; **(Evidence level Ib).** Approval for its use in men with osteoporosis was granted on the basis of a BMD bridging study [199]; **(Evidence level Ib).**

a. Denosumab is contraindicated in patients with hypocalcaemia or with hypersensitivity to any of the constituents of the formulation. Its use is not recommended in pregnancy or in those age <18 years.

b. Hypocalcaemia, as a side-effect of denosumab treatment, increases with the degree of renal impairment; patients should be advised to report symptoms of hypocalcaemia. Pre-existing hypocalcaemia must be investigated and, where due to vitamin D deficiency, treated with vitamin D (e.g., 100,000 to 300,000 IU orally as a loading dose in divided doses) before denosumab treatment is initiated. Adequate intake of calcium and vitamin D is important in all patients, especially those with severe renal impairment.

c. The SPC states all patients should have calcium checked prior to each dose. In patients predisposed to hypocalcaemia (e.g. patients with a creatinine clearance <35 ml/min), serum calcium levels should also be checked within two weeks after the initial dose [200].

d. Side-effects include skin infection, predominantly cellulitis, eczema, hypocalcaemia, and flatulence. Rare adverse effects of denosumab include osteonecrosis of the jaw and atypical femoral fractures and are addressed in Section 7.

e. Denosumab cessation leads to rapid reductions in BMD and elevations in bone turnover to levels above those seen before treatment initiation [201-203]; **(Evidence level Ib)**.

f. Patients who discontinue denosumab have an increased risk of sustaining multiple vertebral fractures. In a post hoc analysis of the FREEDOM study and its extension, women discontinuing denosumab had an increased rate of vertebral fracture over an average of 3-6 months since the last denosumab injection was due. Of those patients who sustained vertebral fractures, 60.7% sustained multiple fractures compared to 38.7% of those discontinuing placebo [204,205]; **(Evidence level Ib).**

g. The increase in vertebral fracture risk following cessation of denosumab therapy emphasises the need to consider continued treatment with an alternative anti-resorptive drug following denosumab withdrawal. An intravenous infusion of 5mg of zoledronate, 6 months after the last denosumab injection, reduces subsequent bone loss [206-210], although this effect is not seen in all patients and may not be maintained beyond one year, particularly in those who have had more than 3 years of denosumab treatment [211] **(Evidence levels IIa and IIb).** Monitoring bone turnover markers at 3 and 6 months post zoledronate infusion can help guide timing of subsequent infusions. Where bone turnover markers are not available, a second infusion of zoledronate after 6 months has been proposed [212]; (**Evidence level IV**). Oral alendronate 70 mg once weekly, was shown to maintain BMD for 12 months in most patients following one year of denosumab therapy, although significant bone loss occurred in a minority [213]; (**Evidence level IIa).** Given the difficulties in stopping denosumab treatment, particularly careful consideration is needed before starting denosumab in younger postmenopausal women, and men.

Anti-resorptive drugs: Hormone replacement therapy (HRT)

HRT comprises a large number of oestrogen formulations or oestrogen plus progestogen combinations, some of which are approved for the prevention of osteoporosis in postmenopausal women at risk of fragility fracture. Conjugated equine oestrogens 0.625mg daily ± 2.5mg/day of medroxyprogesterone acetate has been shown to reduce vertebral, non-vertebral and hip fracture risk in postmenopausal women not selected on the basis of low bone density or high fracture risk [214,215]; **(Evidence level Ib).**

a. The benefit-risk balance of HRT use in postmenopausal women within the age range 53-79 years, was reviewed in 2017. Women using oestrogen-only therapy compared with placebo had significantly lower risk of fractures but significantly higher risk of gall bladder disease, stroke, venous thromboembolism and urinary incontinence. Women using oestrogen plus progestin in combination compared with placebo had significantly lower risk of fractures but had significantly higher risk of invasive breast cancer, probable dementia, gallbladder disease, stroke, urinary incontinence and venous thromboembolism [216]; **(Evidence level Ib).**

b. A more recent narrative review concluded that overall, the benefit-risk profile supports the use of HRT in the management of osteoporosis in women < 60 years old, who have recently (within 10 years) become menopausal, who have menopausal symptoms and have low baseline risk for adverse events [217]; **(Evidence level IIa).**

Anti-resorptive drugs: Calcitriol

Calcitriol (1,25-dihydroxyvitamin D_3) is the active form of vitamin D and is approved for the treatment of established postmenopausal osteoporosis in an oral dose of 0.25µg twice daily. It acts mainly by inhibiting bone resorption. It has been shown to reduce vertebral fracture risk in postmenopausal women with osteoporosis but effects on non-vertebral and hip fractures have not been demonstrated [218]; **(Evidence level IIb).** It is contraindicated in patients with hypercalcaemia or with metastatic calcification. Because calcitriol can cause hypercalcaemia and/or hypercalciuria, serum calcium and creatinine levels should be monitored at 1, 3 and 6 months after starting treatment and at 6 monthly intervals thereafter.

Anti-resorptive drugs: Raloxifene

Raloxifene is a selective oestrogen receptor modulator and inhibits bone resorption. It is approved for the treatment and prevention of osteoporosis in postmenopausal women. Raloxifene has been shown to reduce vertebral fracture risk but reduction in non-vertebral and hip fractures has not been demonstrated [219]; **(Evidence level Ib).**

a. Raloxifene is taken orally as a single daily 60mg dose and may be taken at any time without regard to meals.

b. Raloxifene is contraindicated in women with child-bearing potential, unexplained uterine bleeding, severe hepatic or renal impairment and in women with a history of venous thromboembolism.

c. Side-effects include leg cramps, oedema and vasomotor symptoms. There is a small increase in the risk of venous thromboembolism, mostly within the first few months of treatment and a small increase in the risk of fatal stroke has been reported [220], **(Evidence level IIa)** such that it should be used with caution in women with a history of stroke or with risk factors for stroke disease**.**

d. In the phase III trials, women treated with raloxifene had a significantly decreased risk of developing breast cancer [221]; **(Evidence level Ib).**

Other drugs: Strontium ranelate

Strontium ranelate is taken in a dose of 2g once at night by mouth as a suspension of granules stirred in water, at least two hours after food and/or consumption of calcium containing products. As an alkaline earth metal (closely related to calcium) it substitutes for calcium within hydroxyapatite. Its mode of action is not completely understood but the evidence suggests it has weak anti-resorptive effects whilst maintaining bone formation.

a. In postmenopausal women with osteoporosis, strontium ranelate 2g daily has been shown to reduce the incidence of vertebral and non-vertebral fractures [222,223]; **(Evidence levels Ib).** Fewer hip fractures were reported in a post-hoc analysis of women at high risk of hip fracture (i.e., age ≥74 years with a femoral neck BMD T-score ≤-2.5)

b. Approval for its use in men with osteoporosis was granted on the basis of a BMD bridging study [224]; **(Evidence level Ib).**

c. Common side effects include nausea and diarrhoea.

d. There was a significant increase in venous thromboembolism in the Phase III trials[225].

e. Contraindications include previous myocardial infarction, stroke, or venous thromboembolism as a post-hoc pooled safety analysis showed significant increases in myocardial infarction and “nervous system disorders” including cerebrovascular disease was observed in patients taking strontium ranelate compared to placebo [226].

f. The manufacturer advises against use when the eGFR is <30ml/ml.

g. The higher atomic number of strontium compared with calcium artefactually increases BMD when incorporated into the bone matrix [227]. When strontium ranelate is stopped, this effect is slow to resolve with implications for future BMD monitoring.

Anabolic drugs: Teriparatide (recombinant human parathyroid hormone [PTH] 1-34)

When administered intermittently, teriparatide has anabolic skeletal effects which are most marked in trabecular bone. Teriparatide is approved for the treatment of osteoporosis in postmenopausal women and in men at risk of fragility fracture, and osteoporosis associated with systemic glucocorticoid therapy in women and men at risk of fragility fracture.

a. Teriparatide is given as a subcutaneous injection in a dose of 20 µg/day. The duration of treatment is limited to 24 months.

b. Teriparatide is contraindicated in patients with hypercalcaemia, metabolic bone diseases other than osteoporosis and osteogenesis imperfecta, severe renal impairment, malignant disease affecting the skeleton, prior radiation to the skeleton, and in women who are pregnant or lactating. Teriparatide should be used with caution in patients with moderate renal impairment.

c. PTH levels need to be normal to initiate teriparatide, hence levels should be checked even with normocalcaemia.

d. Side effects include headache, nausea, dizziness, postural hypotension and leg pain. Slight and transient elevations of serum calcium may occur following teriparatide injection.

e. Teriparatide has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis [228]; **(Evidence level Ib).** No primary efficacy end-point data are available for hip fracture incidence, but systematic review and meta-analysis level evidence has shown an OR for hip fracture risk of 0.44 (95% CI: 0.22, 0.87; p=0.019) in patients treated with teriparatide compared with placebo, when considering hip fracture as a safety end point. No significant benefit was seen on upper limb fractures [229]; **(Evidence level Ia).** These findings were further supported by a network meta-analysis of a similar list of RCTs, which reported a HR of 0.35 (95% CI: 0.15, 0.73) for hip fracture in patients treated with teriparatide compared with placebo [230]; **(Evidence level Ia).**

f. Approval for teriparatide use in men with osteoporosis and in men and women with glucocorticoid-induced osteoporosis was granted on the basis of BMD bridging studies [231,232]; **(Evidence level Ib).**

g. Teriparatide biosimilars are now available which is expected to improve the cost-effectiveness of use of generic teriparatide.

Anabolic drugs: Romosozumab

Romosozumab is a humanised monoclonal antibody that binds to and inhibits sclerostin. It has a dual action, stimulating bone formation and inhibiting bone resorption and is approved for the treatment of severe osteoporosis in postmenopausal women at very high risk of fracture. It is currently not approved for use in men. It is given as a subcutaneous injection in a dose of 210 mg (administered as two subcutaneous injections of 105mg each) once monthly. The duration of treatment is limited to 12 months.

a. In postmenopausal women with osteoporosis who received romosozumab 210mg or placebo subcutaneously once monthly for 12 months followed by denosumab 60mg subcutaneously in both groups for 12 months, new vertebral fractures and clinical fractures were significantly reduced in women treated with romosozumab when compared to placebo at 12 months, and at 24 months vertebral fracture rates were significantly lower in women treated with romosozumab during the first 12 months [115]; **(Evidence Level Ib).**

b. In a comparator-controlled study in postmenopausal women with severe osteoporosis subcutaneous romosozumab 210mg once monthly for 12 months followed by oral alendronate 70mg once weekly for 12 months was compared against alendronate 70mg once weekly for 24 months) [116]. New vertebral, non-vertebral, clinical and hip fractures were all significantly lower in women treated with romosozumab followed by alendronate than in those treated with alendronate alone **(Evidence level Ib).** Significantly greater risk reduction in new vertebral and clinical fractures was seen for romosozumab vs. alendronate at 12 months. A significantly higher incidence of cardiovascular events was seen in the romosozumab group compared to the alendronate group [115]; **(Evidence level Ib).**

c. Romosozumab is contraindicated in patients with hypocalcaemia, hypersensitivity to any of the constituents of the formulation, or a history of myocardial infarction or stroke.

d. When determining whether to use romosozumab for an individual patient, both fracture and cardiovascular risk (based on risk factors) over the next year need to be considered.

e. Transient hypocalcaemia has been observed in patients receiving romosozumab. Hypocalcaemia should be corrected prior to initiation of treatment and patients should be adequately supplemented with calcium and vitamin D. Patients with severe renal impairment or on dialysis are at increased risk of developing hypocalcaemia. Osteonecrosis of the jaw and atypical femoral fractures have been very rarely reported with romosozumab use.

Drug treatment for patients with very high fracture risk

Evidence Summary

a. Two randomised comparator-controlled studies in postmenopausal women with severe osteoporosis have demonstrated superior anti-fracture efficacy of skeletal anabolic agents versus anti-resorptive drugs. Subcutaneous romosozumab 210 mg once monthly resulted in significantly greater reduction of vertebral, non-vertebral, clinical and hip fractures at 24 months (risk reduction of 48%, 19%, 27% and 38% respectively) and significantly greater risk reduction in new vertebral and clinical fractures at 12 months when compared to oral alendronate 70 mg once weekly. In the VERtebral fracture treatment comparisons in Osteoporotic women (VERO) study, subcutaneous teriparatide, 20 µg once daily, was associated with significantly fewer new vertebral and clinical fractures than oral risedronate, 35mg once weekly (56% and 52% respectively) after 2 years of treatment [233]; **(Evidence level Ib).** These studies provide the rationale for considering teriparatide or romosozumab as a first-line treatment option in postmenopausal women at very high risk of fracture (see Section 4). Comparator studies of anti-resorptive and anabolic agents have not been reported in men.

b. Following discontinuation of treatment with either teriparatide or romosozumab, bone turnover increases and there is a fall in BMD. Since the maximum permitted duration of treatment with teriparatide is 24 months and with romosozumab 12 months, sequential therapy with anti-resorptive drugs is required to maintain their beneficial skeletal effects.

c. Both alendronate and denosumab have been shown to maintain and increase BMD at the spine and hip following either teriparatide or romosozumab therapy [116,234-237]. In the FRAME extension study, the beneficial effects of 12 months romosozumab therapy on vertebral and non-vertebral fracture risk were maintained when followed by 24 months of denosumab treatment [238]; **(Evidence level IIb)**.

d. When women are switched from oral bisphosphonates to teriparatide or romosozumab, there is attenuation of the increase in spine and hip BMD compared to when these agents are used in treatment-naïve individuals. This blunting effect is greater for teriparatide than romosozumab, especially at the hip [239,240]; **(Evidence level IIb)**. The impact of these effects, if any, on fracture risk is unknown.

e. In women previously treated with denosumab, switching to teriparatide is associated with transient bone loss in the spine and greater and longer lasting bone loss in the hip [235]. When romosozumab is given following denosumab therapy, there is attenuation of the BMD increase at the spine and hip [233,241]; **(Evidence level IIb)**. The impact of these effects, if any, on fracture risk is unknown.

Section 7

Strategies for management of osteoporosis and fracture risk

Duration and monitoring of bisphosphonate treatment

Osteoporosis is a long-term condition for which there is currently no cure, therefore life-long treatment and monitoring to prevent fractures is often required.

Recommendations

1. Plan to prescribe oral bisphosphonates (alendronate, ibandronate and risedronate) for at least 5 years and then re-assess fracture risk. Longer durations of treatment, for at least 10 years, are recommended in the following men and women **(Strong recommendation)** (see Figure 4):
    - 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 5 years of treatment (if treatment is not changed).

2. Plan to prescribe intravenous bisphosphonate (i.e., zoledronate) for at least 3 years and then re-assess fracture risk. Longer durations of treatment, for at least 6 years, are recommended in the following men and women **(Strong recommendation)** (see Figure 5):
    - 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 years of treatment (if treatment is not changed).

3. If a new fracture occurs after bisphosphonate treatment is discontinued, reassess using FRAX and restart treatment **(Strong recommendation).**

4. If bisphosphonate treatment is discontinued and no new fracture occurs, reassess using FRAX after 18 months for risedronate and ibandronate, 2 years for alendronate, and 3 years for zoledronate to inform whether treatment should be restarted **(Strong recommendation).**

Evidence Summary

a. Bisphosphonate therapy is associated with rare but serious adverse events, notably atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ). Defining optimal duration of bisphosphonate therapy attempts to ensure that the benefit in fracture risk reduction outweighs the small risk of AFFs and ONJ at all time points through patient management.

b. Bisphosphonates are retained long term in bone allowing the beneficial effects to persist for some time after cessation of treatment administration. This has raised the possibility that some patients may benefit from a period off treatment to restore the benefit/risk balance [242]; **(Evidence level IIa)**, in which treatment is stopped after some years and the need for reinstitution of therapy is subsequently reassessed. Treatment review in patients taking bisphosphonates is therefore critical [243] and each patient must be assessed individually to assess relative risks and benefits; there is no standard policy for 'all patients' [205]; **(Evidence level IIa).** Because pivotal clinical trials have mostly been limited to a duration of three years, recommendations for longer term use and for pauses in treatment are based on limited evidence from extension studies in postmenopausal women [244,245]; **(Evidence level IIa).** There is currently no evidence on which to base specific recommendations for men.

c. Withdrawal of bisphosphonate treatment is associated with decreases in BMD and increased bone turnover after 2-3 years for alendronate [246,247]; **(Evidence level Ib)**, and 1-2 years for ibandronate and risedronate [248,249]; **(Evidence level Ib).** In the case of zoledronate, withdrawal after 3 years' treatment is associated with only a small decrease in BMD after a further 3 years without treatment [250]; **(Evidence level Ib).** Comparison between offset of alendronate and zoledronate at 3 years showed alendronate-treated patients had greater reductions in total hip BMD and greater rises in PINP, despite a longer treatment exposure with alendronate, supporting a more rapid offset of drug effect than with zoledronate [251]; **(Evidence level IIb).**

d. In the Fracture Intervention Trial Long-term extension study of alendronate (FLEX), there were significantly fewer clinical vertebral fractures in women previously treated with alendronate for 5 years who continued with alendronate for five more years than in those assigned to placebo after 5 years of alendronate [247]; **(Evidence level Ib).** In the Health Outcomes and Reduced Incidence with Zoledronate Once Yearly (HORIZON) study extension, the risk of morphometric vertebral fractures was significantly lower in women continuing on zoledronate for 3 years after the initial three years therapy when compared to those switched to placebo [250]; **(Evidence level Ib).** Post-hoc analyses from the alendronate and zoledronate extension studies suggest that women most likely to benefit from long-term bisphosphonate therapy are those with low hip BMD (T-score <-2.0 in FLEX and ≤-2.5 in HORIZON), those with a prevalent vertebral fracture and those who sustained one or more incident fractures during the initial 3 or 5 years of treatment [70]; **(Evidence level Ib).** Older age was also associated with increased fracture risk after discontinuation of alendronate therapy [252]; **(Evidence level Ib).**

Reassessment of fracture risk in individuals on osteoporosis drug treatment

Recommendations

5. Review treatment adherence in men and women who sustain a fragility fracture whilst on drug treatment, (poor adherence is when less than 80% of treatment has been taken correctly) and investigate for secondary causes of osteoporosis **(Strong recommendation).**
6. Fracture risk assessment in patients receiving drug treatment should be performed using FRAX with BMD, with arithmetic adjustments to FRAX probabilities to take account of additional clinical risk factors (see Section 3). If the FRAX-derived fracture probability exceeds the intervention threshold drug treatment should be continued **(Strong recommendation)**.
7. If biochemical markers of bone turnover indicate relapse from suppressed bone turnover and/or BMD has decreased following bisphosphonate withdrawal, consider resumption of drug treatment (**Conditional recommendation**).
8. After 10 years of bisphosphonate treatment, patient management should be considered on an individual basis (**Conditional recommendation**).

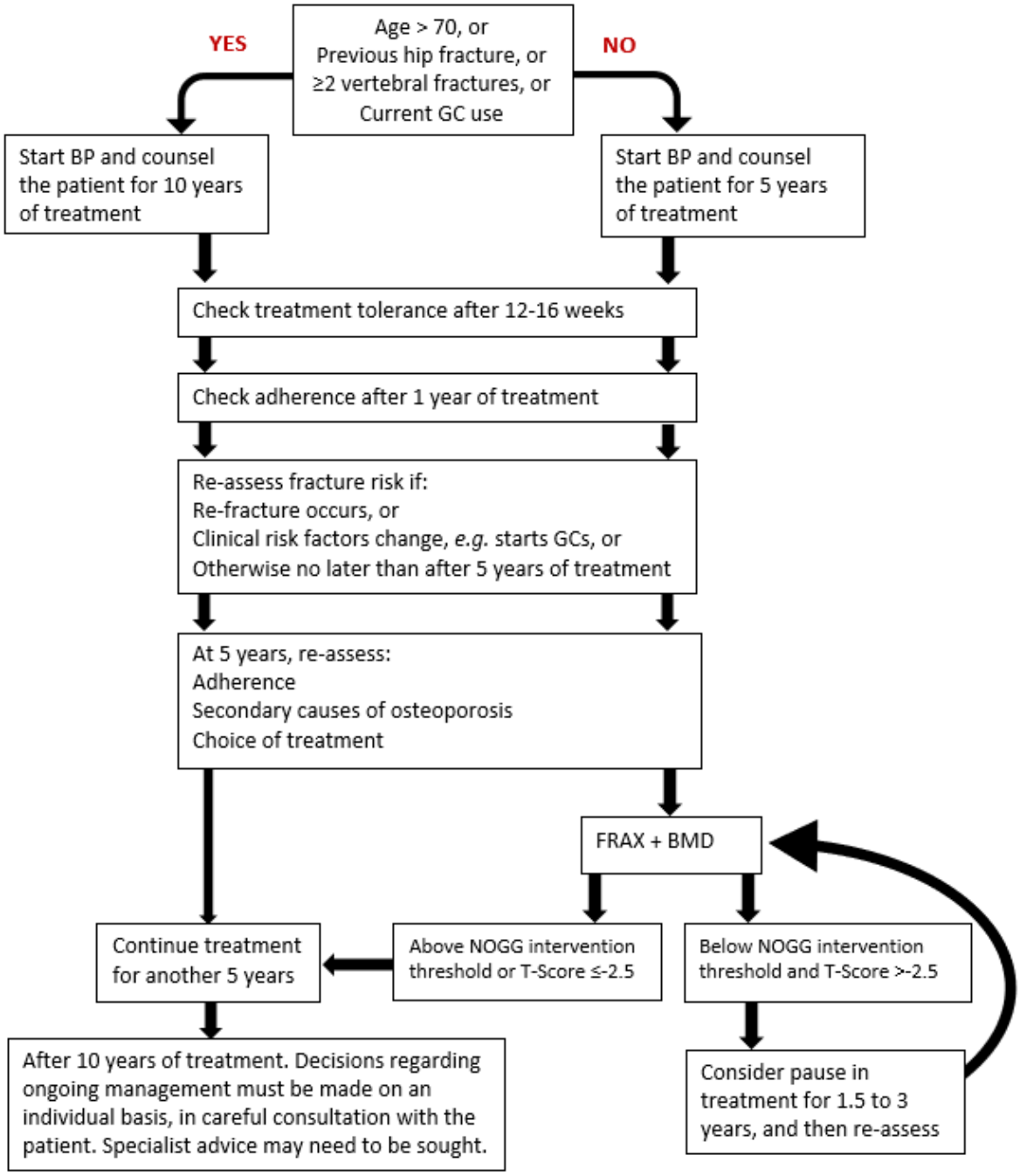
Evidence Summary

a. Stopping osteoporosis treatment, be it with bisphosphonate or denosumab, is associated with an increased risk of fragility fracture, such that routine cessation of anti-resorptive therapy (so called 'drug holidays') is not supported by review of the evidence [205]; **(Evidence level IIa).**

b. Reassessment of fracture risk in treated individuals can be performed using FRAX with femoral neck BMD [141]; **(Evidence level IIb).** The NOGG intervention thresholds can then be used to guide the decision as to whether treatment can be stopped for a period of time (Figures 4 and 5). Whereas FRAX cannot be used to assess treatment response [141]; **(Evidence level IIb)** it does have a role in reassessing current fracture risk to determine the need to continue or to discontinue treatment.

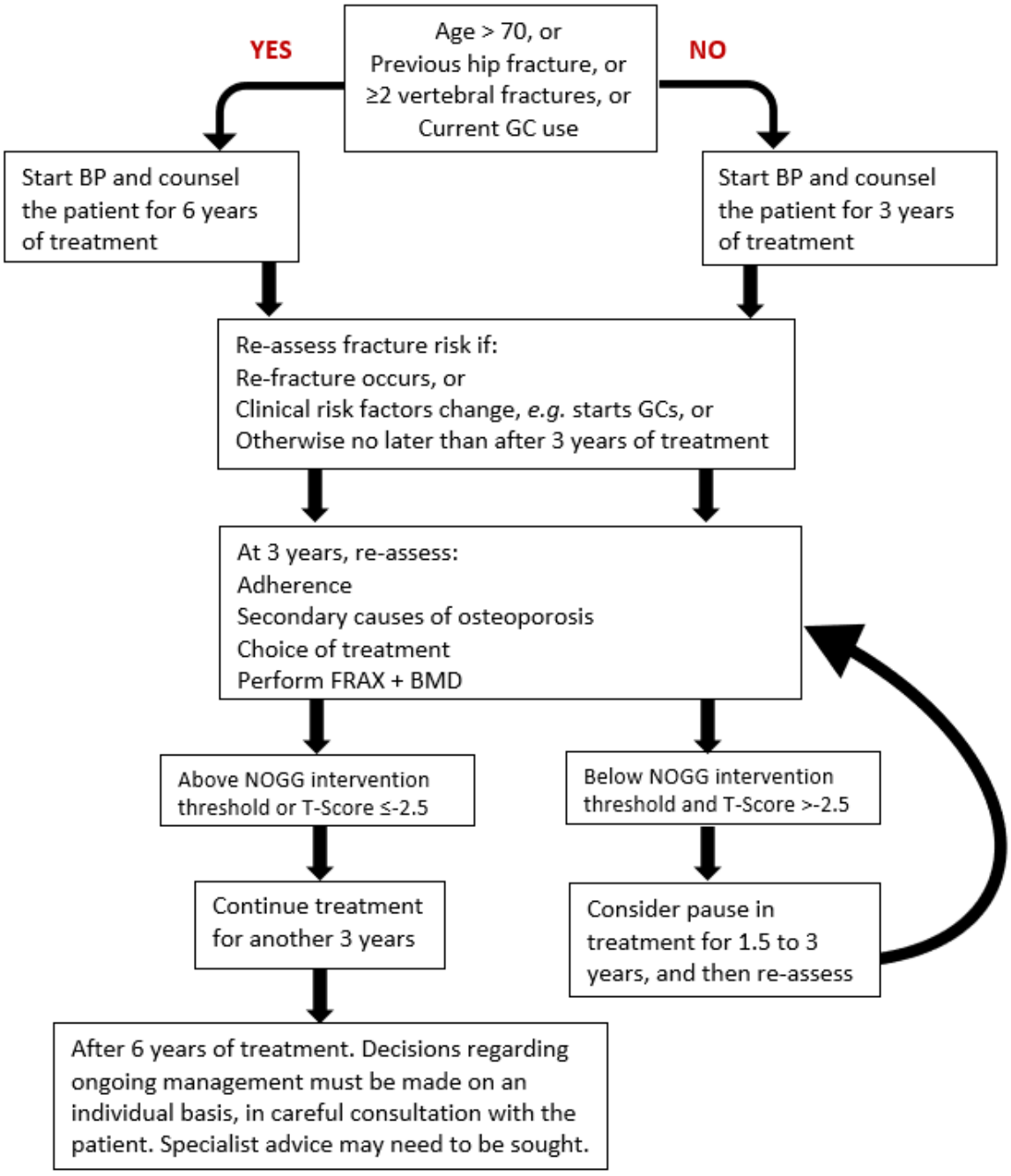
c. Detection of the offset of drug effect, using BMD and bone turnover changes, potentially provides information to influence clinical management. However, there are presently no definitive data that link a potential threshold change in BMD or bone turnover markers during drug offset to clinically meaningful changes in fracture risk.

Figure 4. Oral Bisphosphonates: Clinical Flowchart for long term treatment and monitoring



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

Figure 5. Intravenous Bisphosphonates: Clinical Flowchart for long term treatment and monitoring



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

Rare adverse effects of long-term bisphosphonate and denosumab treatment

Recommendations

9. During bisphosphonate or denosumab therapy, encourage all patients to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling **(Strong recommendation**).
10. In those with severe dental disease who require bisphosphonate or denosumab treatment, timely dental review and dental treatment by an appropriately experienced dental surgeon should be pursued before drug administration, bearing in mind drug treatment should be initiated as soon as possible after a fragility fracture; a multi-disciplinary team (MDT) approach to discuss individual needs is encouraged (**Conditional recommendation**).
11. During bisphosphonate or denosumab treatment, although ideally patients should minimise invasive dental procedures where possible, if indicated they can be carried out safely and successfully in most patients. When dental procedures are required, there are no data available to show whether treatment discontinuation reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment, ensuring patients continue to access routine dental care (**Conditional recommendation**).
12. During bisphosphonate or denosumab therapy, advise patients to report any unexplained thigh, groin or hip pain and if such symptoms develop, the femur should be imaged (by full length femur X-ray, isotope scanning or MRI) **(Strong recommendation**).
13. If an AFF is identified, image the contralateral femur **(Strong recommendation).**
14. All patients who develop an AFF should be referred to an osteoporosis specialist to guide management of future bone health **(Strong recommendation).**
15. In patients who develop an AFF, discontinue bisphosphonate or denosumab treatment (**Conditional recommendation**).

Evidence Summary

a. Osteonecrosis of the jaw (ONJ) occurs only very rarely in patients receiving bisphosphonate or denosumab therapy for osteoporosis. The estimated incidence in those receiving bisphosphonates is 10-100/100,000 person-years of exposure in clinical trials. Risk factors for ONJ include poor oral hygiene, dental disease, dental interventions, smoking, cancer, chemotherapy and/or glucocorticoid therapy [253,254]; **(Evidence level IIa).** The incidence of ONJ is substantially greater with the higher doses of bisphosphonates or denosumab that are used to treat patients with skeletal metastases. The Scottish Dental Clinical Effectiveness Programme has produced guidance on oral health management in patients taking anti-resorptive medication [255].

b. Osteonecrosis of the external auditory canal after bisphosphonate treatment has been described very rarely in case reports, with patients presenting with ear symptoms including chronic ear infections. Possible risk factors include steroid use and chemotherapy and/ or local risk factors such as infection or trauma. [256]; **(Evidence level IV).**

c. Atypical femoral fractures (AFF), mainly of the subtrochanteric and diaphyseal regions of the femoral shaft, have been reported rarely in patients taking bisphosphonates or denosumab for osteoporosis. Asian race, femoral bowing and glucocorticoid use have been identified as risk factors [257]. In a recent review by the ASBMR Task Force on the management of osteoporosis in patients on long-term bisphosphonates, a systematic search of the literature revealed that the absolute risk was consistently low, ranging between 3.2-50 cases/100,000 person-years of exposure [258,259]; **(Evidence level IV).** This estimate appeared to double with prolonged duration of BP use (> 3 years, median duration 7 years), and declined with discontinuation [258,259]; **(Evidence level IV),** [260]; **(Evidence level IIa).**

d. In a nationwide cohort study from Denmark, use of alendronate in excess of 10 years was associated with a 30% lower risk of hip fracture and no increase in the risk of fractures of the subtrochanteric femur and femoral shaft, supporting an acceptable risk benefit balance in terms of fracture outcomes [261]; **(Evidence level IIb).**

e. Atypical femoral fractures are often bilateral, associated with prodromal pain and tend to heal poorly. Prodromal pain can be felt in the thigh, groin or hip for days, weeks or months before fracture. Discontinuation of bisphosphonate or denosumab therapy is advised in patients who develop an atypical fracture, weight-bearing activity should be restricted, adequate calcium and vitamin D should be ensured, and alternative treatment options considered where appropriate. Surgical treatment with intramedullary nailing is often recommended [258,259]; **(Evidence level IV).**

f. There is a lack of good quality evidence on the medical management of bone health following an AFF. However, a recent international expert consensus document supported by a systematic review proposed practical measures to help in patient management [262]; **(Evidence level IV)**. Following an AFF, if risk of fragility fracture is low, further pharmacological bone treatments can be avoided. If fracture risk is high and bilateral surgical fixation of fractures has been performed, consider use of teriparatide. If unilateral or no surgical intervention has taken place, consider teriparatide, romosozumab, raloxifene, or HRT. The potential utility of teriparatide as an adjunct to healing following AFF has been examined. There is no evidence that teriparatide enhances healing of AFFs, but limited data show a tendency towards faster healing in surgically managed AFFs (complete and incomplete). However, in AFFs managed conservatively, there was no suggestion of improved fracture healing with teriparatide [262]; **(Evidence level IV).** The benefits versus risks of using bisphosphonates or denosumab after AFF should be carefully examined if these options are considered, taking into consideration prior unilateral or bilateral nailing, use of an anabolic agent post AFF, together with the overall clinical situation and fracture risk **(Evidence level IV)**.

Glucocorticoid-induced osteoporosis

Recommendations

15. Because bone loss and increased fracture risk occur early after initiation of oral glucocorticoids, bone-protective treatment should be started in the following people, at the same time as glucocorticoid therapy without waiting for bone density assessment, which should follow later **(Strong recommendations)**:

    a) anyone with a prior fragility fracture,

    b) women age ≥70 years,

    c) postmenopausal women, and men age ≥50 years, prescribed high doses of glucocorticoids, i.e., ≥7.5 mg/day of prednisolone or equivalent over 3 months (N.B., this is equivalent to ≥30mg/day of prednisone for 4 weeks over 3 months)

    d) postmenopausal women, and men age ≥50 years, with a FRAX probability of major osteoporotic fracture or of hip fracture exceeding the intervention threshold.

16. Oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate are the most cost-effective first-line drug options for bone protection. Denosumab is an alternative option. Teriparatide can be a first-line drug option in those at very high fracture risk **(Strong Recommendation).**

17. Adequate calcium intake should be achieved through dietary intake if possible, with the use of supplements if necessary. An adequate vitamin D status should be maintained, using supplements if required **(Strong Recommendation).**

18. If glucocorticoid therapy is stopped, withdrawal of bone-protective therapy may be considered at the same time, provided on re-assessment of fracture risk using FRAX, the probabilities of both major osteoporotic fracture and of hip fracture lie below the intervention threshold **(Strong Recommendation)**.

19. If glucocorticoids are continued long term, bone protection should be maintained in the majority of cases **(Strong Recommendation).**

20. Patients starting medium or low dose oral glucocorticoid therapy who have a FRAX probability near to, but below the intervention threshold, should have FRAX with BMD reassessed 12-18 months after starting glucocorticoid therapy (**Conditional recommendation**).

Bone protective therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture, or those receiving high doses of glucocorticoids (≥7.5 mg/day of prednisolone or equivalent over 3 months). Caution is advised when prescribing drug treatment in women of childbearing age. Referral of complex cases to secondary care is often necessary.

Evidence Summary

a. Although guidance on the prevention and management of glucocorticoid-induced osteoporosis has been developed in many countries, there is evidence that in the UK osteoporosis risk assessment and management are still inadequate in long-term users of oral glucocorticoids [263]; **(Evidence level IIIb)**. Bone loss and increased fracture risk occur rapidly after initiation of oral glucocorticoid therapy and increase with the dose of glucocorticoids [55,264]. The increase in fracture risk is seen for vertebral and non-vertebral fractures, including hip fractures, and is partially independent of BMD [56]; **(Evidence level Ia)**.

b. Approval for the use of bone protective therapy to prevent osteoporosis in people receiving oral glucocorticoids was based mainly on BMD bridging studies carried out as part of Phase III randomised controlled trials with bisphosphonates [181,186,193,265,266]. Subsequently approval has been given for denosumab using the same methodology [196]. Fracture prevention has not been considered as an efficacy end-point in most trials. However, although not a primary end-point, in an 18-month randomised controlled trial extended to 36-months comparing teriparatide with alendronate significantly fewer subjects in the teriparatide group had vertebral fractures compared with the alendronate arm [232], but with no benefit on non-vertebral fractures. This protection against vertebral fractures was confirmed in a recent metanalysis which showed that co-prescription of teriparatide, alendronate, risedronate or denosumab with glucocorticoids could reduce the incidence of vertebral fractures, with further evidence of a reduction in non-vertebral fracture rates with alendronate or teriparatide (Table 7) [267]; **(Evidence levels Ia & Ib).**

Table 7. Effect of approved interventions for glucocorticoid-induced osteoporosis on BMD and fracture risk.

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.

c. Considering the increased fracture risk associated with higher glucocorticoid doses, FRAX assessment provides fracture probabilities based on both an average dose of prednisolone (2.5–7.5 mg/day or its equivalent), and a higher dose (≥7.5 mg/day or its equivalent). Individuals taking an average dose of prednisolone <2.5 mg/day will have lower fracture risk, and the average adjustments over all ages in postmenopausal women, and men age ≥50 years, are shown in Table 8 [82]; **(Evidence level IIb)**. For very high doses of glucocorticoids, i.e., >20mg/day prednisolone or its equivalent, greater upward adjustment of fracture probability is required [55]; **(Evidence level IIa)**.

d. When the UK FRAX model is used and the glucocorticoid box is filled, 2 points appear on the NOGG graphs, one for medium dose and one for high dose (all defined as above). The assessment thresholds (fracture probabilities for BMD testing) and intervention thresholds (fracture probabilities for therapeutic intervention) are then used in the same way as described for postmenopausal women and older men.

Table 8. Adjustment of FRAX derived fracture probability estimates according to daily dose of prednisolone

Dose	Prednisolone equivalent dose (mg/day)	Average adjustment to hip fracture probability	Average adjustment to major osteoporotic fracture (MOF) probability
Low	<2.5	-35%	-20%
Medium	2.5-7.5	None	None
High	≥7.5	+20%	+15%

Men receiving androgen-deprivation therapy

Recommendations

The NOGG supports the recent guideline published by Brown et al 2020 [268].

21. All men starting androgen deprivation therapy (ADT) should have their fracture risk assessed using FRAX, considering ADT use as a secondary cause of osteoporosis, with BMD measured where available **(Strong recommendation).**

22. Consider referring men, with high fracture risk requiring drug treatment, to secondary care for assessment and initiation of treatment with bisphosphonates or denosumab **(Conditional recommendation).**

23. Men with FRAX probability near to, but below the intervention threshold, and patients going on to additional systemic therapies (particularly those requiring glucocorticoids), should have FRAX with BMD reassessed 12-18 months after starting ADT (**Conditional recommendation**).

Evidence Summary

a. There is no evidence that skeletal metabolism in men differs fundamentally from that of women [269]. However, secondary causes of osteoporosis are common in men and amongst these hypogonadism is prominent [270]. Androgen deprivation therapy (ADT), used primarily in the treatment of older men with prostate cancer, is frequently associated with hypogonadism. Osteoporosis caused by ADT is associated with rapid loss of BMD within 6–12 months of initiation of ADT [271]; **(Evidence level Ic).** There is a significant increase in fracture risk in men with prostate cancer in the 5 years following the initiation of ADT when compared to those not receiving ADT [272]; **(Evidence level Ic).**

b. Bisphosphonates and denosumab are effective drug treatments for preventing BMD loss in men with prostate cancer taking ADT, although effects on fracture risk have not been demonstrated. Exercise programmes are a less effective alternative which are insufficient in isolation [273]; **(Evidence level Ib).**

c. In a systematic review and network meta-analysis all evaluated treatments for ADT-induced bone loss, which included bisphosphonates and selective oestrogen receptor modulators (SERMs), were effective in improving BMD compared to placebo. However, zoledronate generated greater improvements in BMD compared to other drug treatments at all bone density sites, except for risedronate which had better BMD improvement compared to zoledronate at the femoral neck site in one small study [274]; **(Evidence level IIa).**

d. A recent UK consensus statement on prostate cancer treatment-induced bone loss concluded that fracture risk should be calculated using FRAX, considering ADT use as a secondary cause of osteoporosis, and including BMD where available and practical. BMD should always be assessed where calculated fracture risk is close to the NOGG intervention threshold. Men requiring bone protection drug therapy should be further assessed with referral to secondary care if available and offered appropriate treatment to reduce fracture risk. Those with FRAX probability near to, but below the intervention threshold, and patients going on to additional systemic therapies (particularly those requiring glucocorticoids), should have FRAX with BMD repeated after 12-18 months [268]; **(Evidence level IIa).**

Women receiving aromatase inhibitor therapy

Recommendations

24. All women starting aromatase inhibitor (AI) therapy should have their fracture risk assessed using FRAX, considering AI use as a secondary cause of osteoporosis, including BMD measurement where practical (**Strong recommendation).**
25. Women with high fracture risk should be commenced on drug treatment to prevent osteoporosis and fracture, with bisphosphonates or denosumab (**Strong recommendation).**
26. Women with a FRAX probability near to, but below the intervention threshold, and patients going on to additional systemic therapies (particularly those requiring glucocorticoids), should have FRAX with BMD reassessed 12-24 months after starting AI therapy (**Conditional recommendation**).
27. If adjuvant high-dose bisphosphonate therapy is used as part of breast cancer management, consider assessing fracture risk at the end of this bisphosphonate therapy, particularly if AI therapy continues (**Conditional Recommendation**).

Evidence Summary

a. The use of aromatase inhibitors (AI) in postmenopausal women induces bone loss at an average rate of 1-3% per year at sites rich in trabecular bone. Bone loss is more marked in young women with treatment-induced ovarian suppression, losing an average of 7-8% per annum [275]; **(Evidence level IIa).**

b. In case-control studies the incidence of fracture in women with breast cancer treated with AI is reported to be around 18-20% after 5 years follow-up [276]. NICE guidance on management of early breast cancer, which recognises the excess risk of osteoporosis with the use of AIs, recommends a baseline DXA scan to assess BMD at the time of initiation of AI therapy [277]; **(Evidence level IV).** International Consensus Position Statements suggest that fracture risk should be assessed, although the consideration of AI use as a secondary cause of osteoporosis in FRAX, may not adequately estimate fracture risk [276,278]; **(Evidence level IIa)** with drug treatment to prevent bone loss and fractures recommended in those with a T-score of less than -2, or less than -1.5 with 1 additional risk factor, or in those with 2 or more risk factors (without BMD). Drug treatment should be a bisphosphonate (oral or parenteral) or denosumab, used in the doses as for postmenopausal osteoporosis. Denosumab and zoledronate both lead to significant gains in BMD at the spine and hip in postmenopausal women with breast cancer receiving AI, and both denosumab and risedronate have been shown to reduce fracture risk [279]; **(Evidence level Ia).**

Section 8

Management of symptomatic osteoporotic vertebral fractures

Recommendations

1. Administer analgesia orally rather than parenterally whenever possible. Pain should be regularly reviewed, and analgesia titrated up or down according to pain intensity and side effects, with use of the weakest effective agent for the shortest possible time (**Strong recommendation**).
2. Avoid use of non-steroidal anti-inflammatory drugs (NSAIDs) in older people, but, if used, co-prescribe a proton-pump inhibitor, and monitor for gastro-intestinal, renal and cardiovascular side-effects (**Strong recommendation**).
3. Prescribe appropriate laxative therapy, such as the combination of a stool softener and a stimulant laxative, whenever opioid therapy is used in older people (**Strong recommendation**).
4. It is recommended that exercise programmes following vertebral fracture include progressive muscle strengthening activity, including back extensor muscle strengthening and/or endurance exercise (**Strong recommendation**).
5. When a patient is in pain it may be advisable to initially perform exercise for back extensors in an unloaded position (**Conditional recommendation**).
6. Provide clear and prompt guidance on how to adapt movements involved in day-to-day living, including how exercises can help with posture and pain, to patients with painful vertebral fractures (**Strong recommendation**).
7. Ensure prompt secondary fracture prevention is started following a fracture, with follow-up through fracture liaison services for all postmenopausal women, and men age 50 years and older, with a newly diagnosed vertebral fracture (**Strong recommendation**).

Evidence summary

a. Vertebral fractures can cause acute and chronic pain, height loss, spinal deformity and altered body shape, functional impairment, and reduced health-related quality of life [14]; **(Evidence level Ia).**

b. Analgesia for acute pain is important to allow restoration of function and mobility but must be used safely [280-282]; **(Evidence level IIa).**

c. In patients admitted to hospital, salmon calcitonin given for up to 4 weeks (50-100IU daily given subcutaneously or intramuscularly), has been shown to be an effective adjunctive analgesic for pain, experienced at rest or when walking, associated with acute (within 10 days of) vertebral fracture [283]; **(Evidence level IIa).** However, side-effects (mainly flushing and gastro-intestinal disturbance) are common. Of note long-term use may be associated with an increased risk of cancer [284]. There is no evidence that salmon calcitonin is an effective treatment for chronic pain associated with vertebral fractures [283]; **(Evidence level Ia)**. Of note, in the SPC, calcitonin is indicated for the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, rather than for the management of pain.

d. A single, small, randomised double-blind, controlled trial found 30mg intravenous pamidronate, given within 21 days of acute vertebral fracture, to be more effective than placebo in reducing pain [285]; (**Evidence level IIb**). Of note in the SPC, pamidronate is indicated for the treatment of conditions associated with increased osteoclast activity, rather than for the management of pain.

e. Physiotherapist supervised exercise following vertebral fracture improves pain and physical performance [286]; **(Evidence level Ib).** In the presence of pain it may be advisable to initially perform exercise for back extensors in an unloaded position, such as supine [287]; **(Evidence level Ia).**

f. Combining exercise with physiotherapy-delivered education and guidance can reduce fear of falling and improve psychological symptoms associated with vertebral fractures [163,288]; **(Evidence level Ia).**

g. For patients with painful vertebral fractures, there is low quality evidence suggesting that spinal bracing using soft or rigid external orthoses for 2 hours a day over 6 months may improve pain and trunk muscle strength [287]. There is currently no evidence that bracing with soft or rigid external orthoses improves fracture healing [289]. Hence, routine use of bracing for the treatment of acute or subacute vertebral fractures cannot be recommended **(Evidence level Ia).**

h. The current evidence does not support the routine use of percutaneous vertebroplasty or balloon kyphoplasty for the treatment of painful osteoporotic vertebral fractures, as these procedures do not show consistent patient benefit [287,290]; **(Evidence level Ia).**

i. In older women with vertebral fractures and chronic back pain stable for 6 months or more, a small randomised controlled has shown electrical nerve stimulation, administered as inferential therapy or horizontal therapy five days a week for two weeks, can improve pain over 14 weeks [291]; **(Evidence level IIb).**

j. Patients with a recent vertebral fracture have high imminent risk of further fragility fracture [51]; **(Evidence level IIb).**

k. If a vertebral fracture is associated with impending or existing neurological deficits, urgent referral to spinal surgical services is indicated.

Section 9

Models of care for fracture prevention

Recommendations

1. Multidisciplinary, coordinator-based FLS are recommended to systematically identify men and women with fragility fractures, facilitating timely assessment of fracture and falls risk, and where appropriate, tests to exclude secondary causes of osteoporosis, radiological investigation including BMD testing, and initiation of pharmacological and non-pharmacological interventions to reduce risk of falls and fractures **(Strong recommendation).**
2. FLSs should include embedded local audit systems supported by a clinical fracture database to enable monitoring of care provided to fracture patients [e.g., Royal College of Physicians FLS-Database]; **(Strong recommendation).**
3. FLSs should employ a range of case finding strategies to identify all inpatients and outpatients with fragility fractures **(Strong recommendation).**
4. Diagnostic imaging services should routinely evaluate the spine in all imaging of postmenopausal women, and men age ≥50 years, in which the spine is visualised, and report vertebral fractures using standardised methods **(Strong recommendation).**
5. Patients recommended drug treatment for osteoporosis should be offered tailored information about osteoporosis and its treatments and further medication reviews to support adherence and to discuss alternative treatments if unacceptable adverse events arise or adherence is difficult **(Strong recommendation).**
6. Primary care clinicians should always have in mind the possibility of vertebral fracture in postmenopausal women and men age ≥50 years who present with acute onset back pain, especially thoracic pain, if they have risk factors for osteoporosis (see Section 3) (**Strong recommendation**).

FLS models of care

a. Collaboration between primary care clinicians, secondary care physicians, orthopaedic surgeons, radiologists, and pharmacists and between the medical and non-medical disciplines concerned, should underpin secondary fracture prevention programmes.

b. Fracture Liaison Service (FLS) programmes reduce re-fracture rates and improve survival [292,293] **(Evidence levels Ia and IIb).** The Department of Health and NHS RightCare both state that FLS should be provided for all patients sustaining a fragility fracture [294,295], which aligns with the International Osteoporosis Foundation's global Capture the Fracture® programme [296] and the Royal Osteoporosis Society (ROS) FLS Clinical Standards [297].

c. FLS should provide fully coordinated, intensive models of care for secondary fracture prevention. FLS models which provide identification, assessment and treatment initiation, or a treatment recommendation to primary care, are more clinically effective and cost-effective in improving patient outcomes than approaches that provide identification and/or patient alerts, and/or patient education only [298]; **(Evidence Level Ia).** The required approach is a FLS in which identification, assessment and osteoporosis treatment are all conducted within an integrated electronic health care network, overseen by a coordinator and utilizing a dedicated database measuring performance [296,298-300]**; (Evidence level Ia).**

d. FLS which initiate pharmacological treatment, rather than making a treatment recommendation for primary care initiation, have higher rates of treatment initiation [299]**; (Evidence level Ia).** FLS should also initiate appropriate non-pharmacological interventions and communicate ongoing care effectively with primary care practitioners [297]. FLS should provide a coordinated programme with an integrated approach for falls and fracture prevention; all individuals with a fracture should be fully assessed for falls risk and appropriate interventions to reduce falls should be undertaken [301]. As risk of re-fracture is highest immediately after a fragility fracture, secondary fracture prevention assessment and intervention should be initiated as soon as possible, and no later than 16 weeks post fracture, as recommended by the Royal Osteoporosis Society [51,297].

FLS patient identification

e. FLSs need to employ a range of case finding strategies, to identify both inpatients and outpatients with fragility fractures, and people with vertebral fractures who are often undiagnosed. Reasons for non-identification of vertebral fractures include the absence of a fall as a trigger for investigation, absence of symptoms, or attribution of symptoms to other causes. Furthermore, in patients who do have spinal imaging, use of ambiguous non-standardised terminology in imaging reports, and failure to routinely evaluate the vertebrae captured in imaging of other body systems can both contribute to non-identification of vertebral fractures. The Royal Osteoporosis Society recommend that radiology services should establish local processes to ensure that the spine is routinely evaluated for the presence of vertebral fracture in all available imaging and that reports identifying vertebral fractures should be standardised, using the words 'vertebral fracture', are actionable, and indicate future management [302]; **(Evidence level IV).**

f. Primary care plays an important role in case finding for osteoporotic fractures, particularly vertebral fractures as acute onset back pain, especially thoracic pain, is a common presenting complaint. Targeted use of spinal imaging can help increase case identification, appropriate symptom management, and prompt secondary fracture prevention.

Providing patient information and adherence support

g. Patients identified by any clinical service, to be in need of further intervention, should be offered an explanation of osteoporosis, the causes, consequences and how it can be managed with pharmacological and non-pharmacological interventions. When discussing pharmacological treatment, explanation should be offered for why drug treatment is recommended, the aims and benefits, common and/or severe side effects, the practicalities of taking the medicine and for how long it should be taken [303]; **(Evidence level IV).** The use of decision aids in osteoporosis to support communication of medicine risk-benefit has been shown to improve shared decision making, reduce decisional conflict and improve accuracy of patient perceived fracture risk [304]; **(Evidence level Ib).** Information should be tailored to the needs of the patient to make it accessible and understandable, including provision of written information [305].

h. To promote treatment adherence, healthcare professionals should elicit and address any beliefs and concerns associated with reduced adherence and establish realistic treatment expectations with the patient [303,305]. No one type of intervention has been demonstrated to enhance medicines adherence in osteoporosis care, but multi-component models with active patient engagement have the most positive effects [306,307]; **(Evidence level Ia).** FLS models with a greater number of patient interactions have demonstrated greater clinical effectiveness [300]; **(Evidence level Ia).** The NOGG supports the Royal Osteoporosis Society recommendation to follow-up within 16 weeks and 52 weeks post fracture, to review use of medications that increase the risk of falls and/or fracture, to ensure co-prescription of calcium and vitamin D with bone protective interventions where indicated, to review adverse effects and monitor adherence to therapy [297].

Section 10

Recommendations for training

Recommendations

It is recommended that:

1. Training in personalised care, including shared decision making, is provided within all higher professional training curricula in relevant medicine and surgical specialities (**Strong recommendation**).
2. Training in osteoporosis and metabolic bone diseases is a clearly articulated component of each of the relevant medical and surgical specialities higher professional training curricula set out by the applicable medical and surgical Royal Colleges (**Strong recommendation**).
3. Primary care physicians have sufficient training in this area with efficient access to up-to-date evidence-based resources and guidelines, and continual professional development (CPD) opportunities to maintain and refine knowledge (**Strong recommendation**).
4. The management of osteoporosis is a component of training in all relevant allied health disciplines (**Strong recommendation**).
5. Training should be provided to Fracture Liaison Service personnel to achieve high quality DXA performance and reporting (**Strong recommendation**).
6. Quality improvement training should be provided to healthcare personnel responsible for the delivery of Fracture Liaison and/or Osteoporosis Services (**Strong recommendation**).

Evidence Summary

a. The management of osteoporosis and fragility fracture risk is not subserved by any one specialty. The relevant medical and surgical specialties include general practice, rheumatology, orthopaedic surgery, endocrinology, metabolic medicine, geriatric medicine, and obstetrics and gynaecology. Furthermore, the care of patients with osteoporosis is the responsibility of multiple healthcare professionals, including nurses, physiotherapists, occupational therapists, pharmacists and DXA operators. The multi-disciplinary nature of osteoporosis care offers opportunities for cross-speciality training.

b. It is recognised that primary care is pivotal to the identification of the population at risk of fragility fractures as well as to the long-term management of patients with osteoporosis. It is important that primary care physicians have sufficient training in this area, with access to resources such as updated guidelines and online learning modules to refresh their knowledge.

c. Common to all healthcare roles is a need to provide personalised patient-centred care, a key commitment outlined by the NHS to be achieved by 2023/24. Personalised care is a partnership approach that helps people make informed decisions and choices about their health and wellbeing, working alongside clinical information [Personalised Care Institute 2020].

d. There is significant variability in the access to and quality of DXA services for established FLS worldwide. Despite two decades of training initiatives in osteoporosis densitometry, many centres are falling short of the standards of the IOF-ISCD Osteoporosis Essentials criteria [308].

e. Improving quality of osteoporosis and fracture liaison services is about making health care delivery safe, effective, patient-centred, timely, efficient and equitable. Quality improvement involves the use of a systematic and coordinated approach to solving a problem using specific methods and tools with the aim of bringing about a measurable improvement within a health care setting [309], and can be aided by the use of appropriate Toolkits (e.g. the Royal Osteoporosis Society Fracture Liaison Service Implementation Toolkit).

Examples of appropriate training

Training in Personalised Care

The Personalised Care Institute is a virtual organisation, accountable for setting the standards for evidence-based training in personalised care in England. The Personalised Care Institute Curriculum sets out the standards for training programmes to become accredited with the Personalised Care Institute. The Personalised Care Institute provides eLearning modules for example on Shared Decision Making. The curriculum is designed for health care personnel within primary and secondary care and community teams **https://www.personalisedcareinstitute.org.uk**.

Training in Osteoporosis Management

The Royal Osteoporosis Society Fracture Prevention Practitioner Training is accredited for CPD by RCGP, RCP and RCN. The online training includes five foundation modules and then three advanced modules **https://theros.org.uk/healthcare-professionals/courses-and-cpd/fracture-prevention-practitioner-training/**
The Royal College of General Practice also provides a short e-Learning module on the diagnosis and management of osteoporosis **https://elearning.rcgp.org.uk/course/info.php?id=233**

Training in Musculoskeletal Pain Management

The Health Education England e-Learning for Healthcare Pain Management programme includes training on musculoskeletal pain which encompasses the assessment and management of osteoporotic vertebral fractures **https://www.e-lfh.org.uk/programmes/pain-management/**.

Training in DXA conduct and reporting

The Royal Osteoporosis Society run a Bone Densitometry Foundation Course. This online course provides a foundation in osteoporosis and DXA (**https://theros.org.uk/healthcare-professionals/courses-and-cpd/bone-densitometry-foundation-course/**).

Section 11

Recommendations for commissioners of healthcare

In 2017, the National Falls Prevention Coordination Group with Public Health England (PHE) produced a falls and fracture consensus statement and resource pack with the aim of reducing falls and fracture risk and improving management of fractures, including secondary prevention (https://www.gov.uk/government/publications/falls-and-fractures-consensus-statement). The guidance is aimed at local commissioning and strategic leads in England with a remit for falls, bone health and healthy ageing. Following this, NHS RightCare, working with PHE and the Royal Osteoporosis Society (ROS), developed a Falls and Fragility Fractures Pathway (https://www.england.nhs.uk/rightcare/products/pathways/falls-and-fragility-fractures-pathway/) which defines three priorities that commissioners responsible for falls and fragility fractures should optimise as a priority:

1. Falls prevention
2. Detecting and managing osteoporosis
3. Optimal support after a fragility fracture.

The ROS has developed an online Fracture Liaison Service Implementation Toolkit (https://theros.org.uk/healthcare-professionals/fracture-liaison-services/implementation-toolkit/) designed to enable FLS Commissioning.

In England, the move to Integrated Care Systems (ICS) provides an opportunity to embed enhanced pathways of care for patients at risk of fragility fracture, including imminent fracture risk [310], as part of routine service delivery, for example enabling direct referrals between different secondary care services to streamline patient care pathways.

Where healthcare funding is not delivered through a commissioning structure the recommendations below apply to bodies providing healthcare funding and to local health boards. Thus, in Wales these recommendations apply to the Welsh Government and to local health boards (that are funded directly from the Welsh Government) when setting their Integrated Medium-Term Plans (IMTPs). In Northern Ireland health and social care are integrated and are the responsibility of the Department of Health. Health services are commissioned by the Health and Social Care Board (HSCB) through local commissioning groups from the five Health and Social Care Trusts. Thus, in Northern Ireland these recommendations apply to the HSCB and to the five local commissioning groups.

Recommendations

Based upon the evidence presented in this guideline the NOGG makes the following recommendations to service leaders and/or commissioners of healthcare who:

1. Should recognise that fractures due to osteoporosis are a significant and growing public health issue with consequent high health and social care costs and ensure that fragility fractures are addressed explicitly in their local healthcare programmes (**Strong recommendation**).
2. Should ensure that local healthcare programmes address approaches to reduce the prevalence of avoidable risk factors for osteoporosis and fractures related to falls and poor bone health and, in so doing, makes explicit the roles of both the NHS and other agencies (**Strong recommendation**).
3. Should ensure electronic patient health record systems have FRAX, and the link to the NOGG website, integrated to aid identification and treatment of those at risk of fragility fracture, and that electronic patient health record systems enable clear, and where possible automated, electronic communication between FLS and primary care teams (**Strong recommendation**).
4. Should put arrangements in place so that those at risk of osteoporotic fractures have the opportunity to receive appropriate investigation (e.g., fracture risk assessment, falls risk assessment, bone density measurement), lifestyle advice (e.g., about diet, exercise, and smoking) and bone protective drug therapy [NICE Quality Standards 149, 2017]. The latter includes the availability of parenteral drug therapies in primary care and community healthcare settings (**Strong recommendation**).

5. Should ensure that accurate, up-to-date consistent information about pharmacological drug interventions is widely available to postmenopausal women, and men age ≥50 years, their healthcare advocates and professional advisers, so that patients can make informed decisions about treatment and treatment adherence (**Strong recommendation**).
6. Integrated Care Systems (ICS) should specifically address the burden of fragility fractures on the local economy and ensure that Fracture Liaison Services (see Section 9) are available for all patients who sustain a fragility fracture (**Strong recommendation**).
7. ICS should bring together local specialists, generalists and other stakeholders, including patient representatives, to agree local treatment practices and referral pathways for the management of osteoporosis and prevention of fragility fractures. It is often helpful to identify a lead clinician in both primary and secondary care. The recommendations of this group should take account of local resources and relevant cost-effectiveness data. Local guidelines should be consistent with the evidence presented in this document. Once local guidelines have been agreed, they should be widely disseminated to relevant professionals and potential patients, and the necessary service changes made to allow the guidelines to be implemented. Implementation should be audited and appropriate changes in practice should be instituted where standards are not met with appropriate monitoring of compliance to guidelines thereafter (**Strong recommendation**).

Section 12

Review criteria for audit and quality improvement

Quality standards for osteoporosis

1. Four quality standards for osteoporosis were produced by the National Institute for Health and Care Excellence (NICE) in 2017 (QS149) (https://www.nice.org.uk/guidance/qs149).

2. Seven quality standards for osteoporosis and the prevention of fragility fractures were produced by the Royal Osteoporosis Society in 2017 (https://theros.org.uk/media/0dillsrh/ros-op-standards-november-2017.pdf)

Primary Care

3. Documentation of the proportion of postmenopausal women, and men age ≥50 years, registered with a general practice:

    a) With a fracture code, who have been assessed to determine whether their fracture was a fragility (low-trauma) fracture

    b) With one or more risk factors for fragility fracture, who receive formal fracture risk assessment.

    c) With a prior fragility fracture, who have had a DXA scan with the result recorded.

    d) Calculated to be high or very high risk by FRAX assessment, who have been offered drug treatment.

    e) With an incident hip fracture, those who receive pharmacological drug therapy for osteoporosis within 16 weeks of their fracture.

    f) Who are prescribed pharmacological drug therapy for osteoporosis and who have had confirmed adherence to osteoporosis therapy within the last 12 months.

    g) Who are prescribed pharmacological drug therapy for osteoporosis and have had a 5-year and 10-year review.

    h) Who are prescribed denosumab, who have received timely (within 4 weeks of due date) follow-up injection.

    i) Who are on oral glucocorticoids for ≥3 months who have had a fracture risk assessment.

    j) With documented discussion of fracture risk assessment and a treatment decision.

Fracture Liaison Services

3. The Royal Osteoporosis Society (ROS) published in 2019 six key standards for FLS with a corresponding timeline for the achievement of these six steps, with examples of audit and evidence [297].

4. The Royal College of Physicians Fracture Liaison Service (FLS) Database National Audit (https://www.rcplondon.ac.uk/projects/fracture-liaison-service-database-fls-db) is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the Falls and Fragility Fracture Audit Programme. The FLS-DB is included in the HQIP listing for national audits that must be reported in each English hospital trust's Quality Account, and is required by the Welsh Government for all Health Boards in Wales. These form part of the National Clinical Audit Patient Outcomes Programme. All FLS sites that treat fractures are eligible to participate. The FLS-DB sets out 11 Key Performance Indicators (KPIs) which are designed to measure performance against technology assessments, guidance on osteoporosis and clinical standards for FLSs from the NICE, the ROS and NOGG.

5. The International Osteoporosis Foundation (IOF) Capture the Fracture Best Practice Framework outlines 13 standards for FLS delivery with criteria and targets specified for bronze, silver or gold levels of achievement (https://www.capturethefracture.org/best-practice-framework).

DXA reporting

6. The ROS published in 2019 six quality standards for DXA reporting with a corresponding audit template [39].

Appendix 1

NOGG members

National Osteoporosis Guideline Group

Chair: Celia L Gregson, Professor of Clinical Epidemiology and Honorary Consultant Orthogeriatrician, Musculoskeletal Research Unit, Bristol Medical School, University of Bristol, Bristol, UK and Royal United Hospital NHS Foundation Trust, Bath, UK.

The guideline development writing group was composed of two committees, the Guideline Development Group and the Expert Advisory Group. Members of both committees contributed to the content of the guideline, but consensus agreement on the recommendations was restricted to the Guideline Development Group. Disclosures of potential conflicts of interest of all members are available on the NOGG website (www.nogg.org.uk). No funding source/body was involved in the development and/or writing of this guideline, all members gave up their time voluntarily, without any renumeration for their work.

Guideline Development Group

- Juliet Compston, Cambridge Biomedical Campus, Cambridge.
- John Edwards, Senior Lecturer in General Practice, Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, and General Practitioner, Wolstanton Medical Centre, Newcastle under Lyme.
- John A Kanis, Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia and Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield.
- Sarah Leyland, Clinical adviser and Osteoporosis Specialist Nurse, Royal Osteoporosis Society
- Rebecca Low, General Practitioner, Marcham Road Health Centre, Abingdon and Specialty Doctor in Metabolic Bone Disease, Nuffield Orthopaedic Centre, Oxford.
- Zoe Paskins, School of Medicine, Keele University, Keele, and Haywood Academic Rheumatology Centre, Haywood Hospital, Midlands Partnership NHS Foundation Trust, Stoke-on-Trent.
- Julia Thomson, Nurse manager and Osteoporosis Specialist Nurse, Royal Osteoporosis Society.
- Nic Vine, Public and patient representative.
- Jane Parker, Public and patient representative (since 2021)
- Jean Bowden, Public and patient representative (since 2021)

Past members:

- Penny Ritchie Calder (MBE), Public and patient representative (stepped down 2020).
- David Brookfield, Public and patient representative (stepped down 2021).

Expert Advisory Group

- David Armstrong, Consultant Rheumatologist, Western Health and Social Care Trust (NI), and Visiting Professor, Nutrition Innovation Centre for Food and Health, Ulster University.
- Cyrus Cooper, Professor of Rheumatology, MRC Lifecourse Epidemiology Unit, University of Southampton and Professor of Musculoskeletal Science, University of Oxford.
- Neil Gittoes, Consultant & Honorary Professor of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham & University of Birmingham, Centre for Endocrinology, Diabetes and Metabolism, Birmingham.
- Nicholas C Harvey, Professor of Rheumatology and Clinical Epidemiology, MRC Lifecourse Epidemiology Unit, University of Southampton.

- Eugene McCloskey, Professor in Adult Bone Disease and Honorary Consultant, University of Sheffield and Director of the Centre for Integrated research in Musculoskeletal Ageing (CIMA), University of Sheffield.
- Katie Moss, Consultant Rheumatologist and Honorary Senior Lecturer, St George's University Hospital, London.
- Ken Poole, Reader in Metabolic Bone Disease, Honorary Consultant Physician (Rheumatology), Department of Medicine, University of Cambridge.
- David Reid, Emeritus Professor of Rheumatology, University of Aberdeen.
- Mike Stone, Consultant Physician (Geriatric Medicine), University Hospital Llandough, and Director of Bone Research, Cardiff and Vale University Health Board.

Temporarily seconded away from NOGG

- Peter Selby, Endocrinologist, Consultant Physician and Honorary Clinical Professor of Metabolic Bone Disease, University of Manchester (seconded away from NOGG for 2020-21).

Appendix 2

Stakeholders

List of stakeholders

- Association for Clinical Biochemistry and Laboratory Medicine
- Bone Research Society
- British Geriatrics Society
- British Orthopaedic Association
- British Orthopaedic Research Society
- British Menopause Society
- British Society for Rheumatology
- European Calcified Tissues Society
- European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
- International Osteoporosis Foundation
- Osteoporosis 2000
- Osteoporosis Dorset
- Primary Care Rheumatology and Musculoskeletal Medicine Society
- Royal College of Physicians
- Royal Osteoporosis Society
- Royal Pharmaceutical Society
- Society for Endocrinology
- The Nutrition Society

External reviewers

1. William Leslie, University of Manitoba, Canada
2. Nicola Peel, Sheffield Teaching Hospitals NHS Foundation Trust, UK
3. Stephen Tuck, South Tees Hospitals NHS Foundation Trust, UK

Disclosures of interest

Disclosures of potential conflicts of interest of external reviewers are available on the NOGG website (www.nogg.org.uk)

Appendix 3

Grading of 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)
IIa	systematic review of at least one non-randomised controlled trial or well-designed cohort study
IIb	individual cohort study or low quality RCTs
IIIa	systematic review of at least one case-controlled study
IIIb	individual case-control study
IV	expert committee reports or opinions and/or clinical experience of authorities, case series (and poor-quality cohort and case-control studies)

Levels of evidence for validity of candidate risk factors

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
Ic	Level I studies (with appropriate populations and internal controls)
IIa	Systematic reviews or meta-analysis of level II studies
IIb	Level II studies (inappropriate population or lacking an internal control)
IIIa	Systematic reviews or meta-analysis of level III studies
IIIb	Case-control studies
IV	Evidence from expert committees without explicit critical scientific analysis or that based on physiology, basic research or first principles.

Of note, FRAX risk factors are all grade A or B according to evidence for reversibility of risk [63].

Grading of recommendations

Recommendations follow the Grading of Recommendations Assessment, Development, and Evaluation GRADE binary classification of recommendations as either strong or conditional (also known as discretionary or qualified recommendations) [311]. Recommendations have been made after assessment of [312]:
The balance between desirable and undesirable effects -The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted.
The quality of evidence - The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences - The more variability/ uncertainty in values and preferences the more likely a conditional recommendation is warranted.
Costs (resource allocation) - The higher the costs of an intervention (**i.e.,** the more resources consumed) the more likely a conditional recommendation is warranted.

For example, a strong recommendation applies where the clinician considers that most people ought to receive the intervention, or where adherence to the recommendation could be used as a performance or quality indicator and that deviation from this recommendation would prompt documentation of a clinician's rationale. NICE suggests using 'offer' (or similar action wording such as 'measure', 'advise', 'commission' or 'refer') when describing a strong recommendation [313].

A conditional recommendation applies where the clinician examines the evidence and prepares to discuss this with the patient together with the patient's values and preferences, or where documentation of the discussion of the pros and cons of an intervention is the indicator of quality, rather than the course of action itself. NICE suggests using wording such as 'consider' when describing conditional recommendations.
Where insufficient evidence is available or the evidence available is equivocal, recommendations are not made.

Appendix 4

AMSTAR2 grading of systematic reviews and meta-analyses

The quality of systematic reviews and meta-analyses used in the formulation of recommendations was assessed using AMSTAR2 (https://amstar.ca/Amstar-2.php).

Section	Reference	Type of study	AMSTAR2 grading	Reference
3. Fracture risk assessment and case finding	Bai et al 2020	MA	Low	59
	Gausden et al 2017	SR	Medium	101
	Johannesdottir et al 2018	SR	Low	41
	Kanis et al 2016	SR	Medium	78
	Marshall et al 1996	MA	Critically Low	28
	Merlijn et al 2019	SR & MA	Critically Low	108
	Mortensen et al 2020	SR & MA	Medium	65
	Singh-Ospina et al 2017	SR & MA	Low	72
	Vilaca et al 2020	SR & MA	Low	58
	Zhang et al 2020	SR & MA	Low	110
4. Intervention thresholds and management strategy	Kanis et al 2016	SR	Medium	78
5. Non-pharmacological management of osteoporosis	Babatunde et al 2020	SR & MA	Medium	161
	El-Khoury et al 2013	SR & MA	Medium	167
	Darling et al 2019	SR & MA	Medium	145
	Fabiani et al 2019	SR & MA	Medium	142
	Gillespie et al 2012	SR & MA	High	171
	Groenendijk et al 2019	SR & MA	Medium	144
	Iguacel et al 2018	SR & MA	High	147
	Howe et al 2011	SR & MA	High	159
	Jepsen et al 2017	SR & MA	Medium	172
	Kahwati et al 2018	SR & MA	Medium	156
	Kelley et al 2000	SR & MA	Medium	162
	Kemmler et al 2020	SR & MA	Low	160
	Kunutsor et al 2018	SR & MA	Medium	164
	Min et al 2017	SR & MA	Low	175
	Shen et al 2015	SR & MA	Medium	174
	Sherrington et al 2017	SR & MA	Low	170
	Sherrington et al 2019	SR & MA	High	168
	Yao et al 2019	SR & MA	Medium	152
	Zhao et al 2019	SR & MA	Low	169

6. Pharmacological treatment options	Diez-Perez et al 2019	SR & MA	Medium	229
	Gartlehner et al 2017	SR & MA	Medium	216
	Nayak et al 2017	SR & MA	Low	314
	Poon et al 2018	SR & MA	Low	274
	Simpson et al 2020	SR & MA	Medium	230
	Zeng et al 2019	SR & MA	Medium	315
7. Strategies for management of osteoporosis and fracture risk	Deng et al 2020	SR & MA	Low	267
	Dennison et al 2019	SR	Medium	205
	Gedmintas et al 2013	SR & MA	Medium	260
	Khan et al 2015	SR	Medium	253
	Miyashita et al 2020	SR & MA	Low	279
	Nayak et al 2019	SR & MA	High	242
	Tsourdi et al 2020	SR	Medium	203
	Wang et al 2018	SR & MA	Critically Low	316
	Yanbeiy et al 2019	SR & MA	Low	317
8. Management of symptomatic osteoporotic vertebral fractures	Al-Sari et al 2016	SR & MA	Low	14
	British Geriatric Society 2013	SR	Medium	282
	Buchbinder et al 2018	SR & MA	High	290
	Ebeling et al 2019	SR & MA	Critically Low	287
	Gibbs et al 2019	SR	Medium	286
	Hofler et al 2020	SR	Low	289
	Knopp-Sihota et al 2012	SR & MA	Medium	283
	Svensson et al 2017	SR	Low	288
9. Models of care for fracture prevention	Ganda et al 2013	SR & MA	Critically Low	298
	Ganda et al 2019	SR & MA	Low	299
	Martin et al 2020	SR & MA	Medium	307
	Paskins et al 2020	SR	Medium	304
	Wu et al 2018	SR	Critically Low	293
	Wu et al 2018	SR & MA	Low	300

SR; Systematic Review. MA; Meta-analysis

References

1. Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 2009; **62**(2): 105-8.
2. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013; **75**(4): 392-6.
3. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 2017; **12**(1): 43.
4. Harvey NC, McCloskey E, Kanis JA, Compston J, Cooper C. Cost-effective but clinically inappropriate: new NICE intervention thresholds in osteoporosis (Technology Appraisal 464). Osteoporos Int 2018; **29**(7): 1511-3.
5. Söreskog E, Lindberg I, Kanis JA, et al. Cost-effectiveness of romosozumab for the treatment of postmenopausal women with severe osteoporosis at high risk of fracture in Sweden. Osteoporos Int 2021; **32**(3): 585-94.
6. Kanis JA, Melton LJ, 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994; **9**(8): 1137-41.
7. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. Bone 2001; **29**(6): 517-22.
8. Borgström F, Karlsson L, Ortsäter G, et al. Fragility fractures in Europe: burden, management and opportunities. Archives of Osteoporosis 2020; **15**(1): 59.
9. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip Fracture in Women without Osteoporosis. Journal of Clinical Endocrinology Metabolism 2005; **90**(5): 2787-93.
10. Schuit SCE, van der Klift M, Weel AEAM, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 2004; **34**(1): 195-202.
11. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 2007; **18**(8): 1033-46.
12. Royal College of Physicians. National Hip Fracture Database Annual Report. **https://www.nhfd.co.uk/files/2019ReportFiles/NHFD_2019_Annual_Report_v101.pdf**, 2019.
13. NHS National Services Scotland. Scottish Hip Fracture Audit. Hip Fracture Care Pathway Report 2019. **https://www.shfa.scot.nhs.uk/Reports/_docs/2019-08-20-SHFA-Report.pdf**, 2019.
14. Al-Sari UA, Tobias J, Clark E. Health-related quality of life in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis. Osteoporos Int 2016; **27**(10): 2891-900.
15. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of life in a United Kingdom hip fracture population. The Warwick Hip Trauma Evaluation--a prospective cohort study. Bone Joint J, 2015; **97-b**(3): 372-82.
16. Leal J, Gray AM, Prieto-Alhambra D, et al. Impact of hip fracture on hospital care costs: a population-based study. Osteoporos Int 2016; **27**(2): 549-58.
17. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos 2021; **doi.org/10.1007/s11657-020-00871-9**.
18. Royal College of Physicians. National Hip Fracture Database Annual Report. **https://www.nhfd.co.uk/files/2018ReportFiles/NHFD-2018-Annual-Report-v101.pdf**, 2018.
19. Royal College of Physicians. The challenge of the next decade: are hip fracture services ready? A review of data from the National Hip Fracture Database (January–December 2019). London: RCP, 2021.
20. Hawley S, Javaid MK, Prieto-Alhambra D, et al. Clinical effectiveness of orthogeriatric and fracture liaison service models of care for hip fracture patients: population-based longitudinal study. Age Ageing 2016; **45**(2): 236-42.
21. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. Jama 2009; **301**(5): 513-21.
22. Johnell O, Kanis JA, Odén A, et al. Mortality after osteoporotic fractures. Osteoporos Int 2004; **15**(1): 38-42.

23. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone 2003; **32**(5): 468-73.

24. Bhimjiyani A, Neuburger J, Jones T, Ben-Shlomo Y, Gregson CL. The effect of social deprivation on hip fracture incidence in England has not changed over 14 years: an analysis of the English Hospital Episodes Statistics (2001-2015). Osteoporos Int 2018; **29**(1): 115-24.

25. Bhimjiyani A, Neuburger J, Jones T, Ben-Shlomo Y, Gregson CL. Inequalities in hip fracture incidence are greatest in the North of England: regional analysis of the effects of social deprivation on hip fracture incidence across England. Public Health 2018; **162**: 25-31.

26. Curtis EM, van der Velde R, Moon RJ, et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone 2016; **87**: 19-26.

27. van der Velde RY, Wyers CE, Curtis EM, et al. Secular trends in fracture incidence in the UK between 1990 and 2012. Osteoporosis International 2016; **27**(11): 3197-206.

28. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; **312**(7041): 1254-9.

29. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res 2005; **20**(7): 1185-94.

30. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002; **359**(9321): 1929-36.

31. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. OsteoporosInt 2000; **11**(3): 192-202.

32. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone 2008; **42**(3): 467-75.

33. De Laet CE, Van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Hip fracture prediction in elderly men and women: validation in the Rotterdam study. J Bone Miner Res 1998; **13**(10): 1587-93.

34. Binkley N, Adler R, Bilezikian JP. Osteoporosis diagnosis in men: the T-score controversy revisited. Curr Osteoporos Rep 2014; **12**(4): 403-9.

35. International Society for Clinical Densitometry (ISCD). Adult Official Positions of the ISCD. **https://iscd.org/learn/official-positions/adult-positions/**, 2019.

36. Kanis JA, Johnell O, Oden A, et al. The use of multiple sites for the diagnosis of osteoporosis. Osteoporos Int 2006; **17**(4): 527-34.

37. Leslie WD, Tsang JF, Caetano PA, Lix LM. Number of osteoporotic sites and fracture risk assessment: a cohort study from the Manitoba Bone Density Program. J Bone Miner Res 2007; **22**(3): 476-83.

38. Leslie WD, Martineau P, Bryanton M, Lix LM. Which is the preferred site for bone mineral density monitoring as an indicator of treatment-related anti-fracture effect in routine clinical practice? A registry-based cohort study. Osteoporos Int 2019; **30**(7): 1445-53.

39. Royal Osteoporosis Society. Reporting dual energy X-ray absorptiometry scans in adult fracture risk assessment: Standards for quality. **https://theros.org.uk/media/xhfhyy52/ros-reporting-dxa-scans-in-adult-fracture-risk-assessment-august-2019.pdf**, 2019.

40. Adams AL, Fischer H, Kopperdahl DL, et al. Osteoporosis and Hip Fracture Risk From Routine Computed Tomography Scans: The Fracture, Osteoporosis, and CT Utilization Study (FOCUS). J Bone Miner Res 2018; **33**(7): 1291-301.

41. Johannesdottir F, Allaire B, Bouxsein ML. Fracture Prediction by Computed Tomography and Finite Element Analysis: Current and Future Perspectives. Curr Osteoporos Rep 2018; **16**(4): 411-22.

42. Pickhardt PJ, Bodeen G, Brett A, Brown JK, Binkley N. Comparison of femoral neck BMD evaluation obtained using Lunar DXA and QCT with asynchronous calibration from CT colonography. J Clin Densitom 2015; **18**(1): 5-12.

43. Cann CE, Adams JE, Brown JK, Brett AD. CTXA hip--an extension of classical DXA measurements using quantitative CT. PloS one 2014; **9**(3): e91904-e.

44. Ziemlewicz TJ, Maciejewski A, Binkley N, Brett AD, Brown JK, Pickhardt PJ. Opportunistic Quantitative CT Bone Mineral Density Measurement at the Proximal Femur Using Routine Contrast-Enhanced Scans: Direct Comparison With DXA in 355 Adults. J Bone Miner Res 2016; **31**(10): 1835-40.

45. Lenchik L, Weaver AA, Ward RJ, Boone JM, Boutin RD. Opportunistic Screening for Osteoporosis Using Computed Tomography: State of the Art and Argument for Paradigm Shift. Current rheumatology reports 2018; **20**(12): 74.
46. Kanis JA on behalf of the WHO Scientific Group. Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK, Sheffield 2008, 2007.
47. Laet C, Kanis J, Oden A, et al. Body mass index as a predictor of fracture risk: A meta-analysis. Osteoporosis International 2005; **16**(11): 1330-8.
48. Leslie WD, Schousboe JT, Morin SN, et al. Fracture risk following high-trauma versus low-trauma fracture: a registry-based cohort study. Osteoporos Int 2020; **31**(6): 1059-67.
49. Kanis J, Johnell O, Laet CD, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004; **35**: 375-82.
50. Johansson H, Odén A, McCloskey EV, Kanis JA. Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures. Osteoporosis International 2014; **25**(1): 235-41.
51. Kanis JA, Johansson H, Odén A, et al. Characteristics of recurrent fractures. Osteoporos Int 2018; **29**(8): 1747-57.
52. Kanis JA, Johansson H, Harvey NC, et al. Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. Osteoporos Int 2020; **31**(10): 1817-28.
53. Kanis JA, Johansson H, Oden A, et al. A family history of fracture and fracture risk: a meta-analysis. Bone 2004; **35**(5): 1029-37.
54. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. Osteoporos Int 2005; **16**(2): 155-62.
55. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford) 2000; **39**(12): 1383-9.
56. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Mineral Research: 2004; **19**(6): 893-9.
57. Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. Osteoporos Int 2005; **16**(7): 737-42.
58. Vilaca T, Schini M, Harnan S, et al. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: A systematic review and meta-analysis update. Bone 2020; **137**: 115457.
59. Bai J, Gao Q, Wang C, Dai J. Diabetes mellitus and risk of low-energy fracture: a meta-analysis. Aging clinical and experimental research 2020; **32**(11): 2173-86.
60. Leslie WD, Rubin MR, Schwartz AV, Kanis JA. Type 2 diabetes and bone. Journal of Bone and Mineral Research 2012; **27**: 2231-7.
61. Giangregorio LM, Leslie WD, Lix LM, et al. FRAX underestimates fracture risk in patients with diabetes. Journal of Bone and Mineral Research 2012; **27**(2): 301-8.
62. Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E. BMD, clinical risk factors and their combination for hip fracture prevention. Osteoporos Int 2009; **20**(10): 1675-82.
63. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD. FRAX(®) with and without bone mineral density. Calcif Tissue Int 2012; **90**(1): 1-13.
64. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001; **344**(5): 333-40.
65. Mortensen SJ, Mohamadi A, Wright CL, et al. Medications as a Risk Factor for Fragility Hip Fractures: A Systematic Review and Meta-analysis. Calcif Tissue Int 2020; **107**(1): 1-9.
66. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with parkinsonism and anti-Parkinson drugs. Calcif Tissue Int 2007; **81**(3): 153-61.
67. Arbouw ME, Movig KL, van Staa TP, Egberts AC, Souverein PC, de Vries F. Dopaminergic drugs and the risk of hip or femur fracture: a population-based case-control study. Osteoporos Int 2011; **22**(7): 2197-204.
68. Lee YK, Lee EG, Kim HY, et al. Osteoporotic Fractures of the Spine, Hip, and Other Locations after Adjuvant Endocrine Therapy with Aromatase Inhibitors in Breast Cancer Patients: a Meta-analysis. Journal of Korean medical science 2020; **35**(46): e403.

69. Myint ZW, Momo HD, Otto DE, Yan D, Wang P, Kolesar JM. Evaluation of Fall and Fracture Risk Among Men With Prostate Cancer Treated With Androgen Receptor Inhibitors: A Systematic Review and Meta-analysis. JAMA network open 2020; **3**(11): e2025826.

70. Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? The Journal of clinical endocrinology and metabolism 2014; **99**(12): 4546-54.

71. Palermo A, D'Onofrio L, Eastell R, Schwartz AV, Pozzilli P, Napoli N. Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review. Osteoporos Int 2015; **26**(8): 2073-89.

72. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, et al. Effect of Sex Steroids on the Bone Health of Transgender Individuals: A Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 2017; **102**(11): 3904-13.

73. Diez-Perez A, Adachi JD, Agnusdei D, et al. Treatment failure in osteoporosis. Osteoporos Int 2012; **23**(12): 2769-74.

74. Lorentzon M, Branco J, Brandi ML, et al. Algorithm for the Use of Biochemical Markers of Bone Turnover in the Diagnosis, Assessment and Follow-Up of Treatment for Osteoporosis. Adv Ther 2019; **36**(10): 2811-24.

75. Johansson H, Odén A, Kanis JA, et al. A meta-analysis of reference markers of bone turnover for prediction of fracture. Calcif Tissue Int 2014; **94**(5): 560-7.

76. Kanis JA, Johansson H, Harvey NC, et al. The use of 2-, 5-, and 10-year probabilities to characterize fracture risk after a recent sentinel fracture. Osteoporos Int 2021; **32**(1): 47-54.

77. McCloskey EV, Borgström F, Cooper C, et al. Short time horizons for fracture prediction tools: time for a rethink. Osteoporos Int 2021: in press.

78. Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, McCloskey EV. A systematic review of intervention thresholds based on FRAX : A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos 2016; **11**(1): 25.

79. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. 2009; **339**: b4229.

80. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. NICE clinical guideline [CG146]. Manchester: NICE. **www.nice.org.uk/guidance/cg146**, 2012.

81. National Institute for Health and Care Excellence (NICE). Osteoporosis: Quality standard [QS149]. Manchester, NICE, 2017.

82. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011; **22**(3): 809-16.

83. Leslie WD, Morin S, Lix LM, et al. Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporos Int 2012; **23**(1): 75-85.

84. Johansson H, Kanis JA, Odén A, et al. Impact of femoral neck and lumbar spine BMD discordances on FRAX probabilities in women: a meta-analysis of international cohorts. Calcified Tiss Inter 2014; **95**(5): 428-35.

85. McCloskey EV, Odén A, Harvey NC, et al. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. J Bone Mineral Res 2016; **31**(5): 940-8.

86. Leslie WD, Lix LM, Morin SN, et al. Adjusting Hip Fracture Probability in Men and Women Using Hip Axis Length: the Manitoba Bone Density Database. J Clin Densitom 2016; **19**(3): 326-31.

87. Masud T, Binkley N, Boonen S, Hannan MT. Official Positions for FRAX® clinical regarding falls and frailty: can falls and frailty be used in FRAX®? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. J Clin Densitom 2011; **14**(3): 194-204.

88. Johansson H, Odén A, Lorentzon M, et al. Is the Swedish FRAX model appropriate for Swedish immigrants? Osteoporos Int 2015; **26**(11): 2617-22.

89. Leslie WD, Johansson H, McCloskey EV, Harvey NC, Kanis JA, Hans D. Comparison of Methods for Improving Fracture Risk Assessment in Diabetes: The Manitoba BMD Registry. J Bone Mineral Res, 2018; **33**(11): 1923-30.

90. Wändell P, Li X, Carlsson AC, Sundquist J, Sundquist K. Osteoporotic fractures among foreign-born individuals: a national Swedish study. Osteoporosis International 2021; **32**(2): 343-52.

91. Brennan SL, Leslie WD, Lix LM, et al. FRAX provides robust fracture prediction regardless of socioeconomic status. Osteoporos Int 2014; **25**(1): 61-9.

92. Leslie WD, Orwoll ES, Nielson CM, et al. Estimated lean mass and fat mass differentially affect femoral bone density and strength index but are not FRAX independent risk factors for fracture. J Bone Mineral Res 2014; **29**(11): 2511-9.

93. Whitlock RH, Leslie WD, Shaw J, et al. The Fracture Risk Assessment Tool (FRAX®) predicts fracture risk in patients with chronic kidney disease. Kidney Int 2019; **95**(2): 447-54.

94. Baruch Fischhoff, Noel T. Brewer, Downs. JS. Communicating Risks and Benefits: An Evidence-Based User's Guide: US Department of Health and Human Services Food and Drug Administration.; 2018.

95. Excellence. NIfHaC. NICE guideline [NG132]: Hyperparathyroidism (primary): diagnosis, assessment and initial management. **https://www.nice.org.uk/guidance/ng132/chapter/Recommendations#diagnostic-testing-in-primary-care**, 2019.

96. Fink HA, Milavetz DL, Palermo L, et al. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J Bone Miner Res 2005; **20**(7): 1216-22.

97. Melton LJ, 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. Osteoporos Int 1999; **10**(3): 214-21.

98. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. Jama 2001; **285**(3): 320-3.

99. Jang HD, Kim EH, Lee JC, Choi SW, Kim K, Shin BJ. Current Concepts in the Management of Osteoporotic Vertebral Fractures: A Narrative Review. Asian Spine J 2020; **14**(6): 898-909.

100. Lewiecki EM. Bone densitometry and vertebral fracture assessment. Curr Osteoporos Rep 2010; **8**(3): 123-30.

101. Gausden EB, Nwachukwu BU, Schreiber JJ, Lorich DG, Lane JM. Opportunistic Use of CT Imaging for Osteoporosis Screening and Bone Density Assessment: A Qualitative Systematic Review. J Bone Joint Surg Am 2017; **99**(18): 1580-90.

102. Bromiley PA, Clark EM, Poole KE. Computer-Aided Diagnostic Systems for Osteoporotic Vertebral Fracture Detection: Opportunities and Challenges. J Bone Mineral Research 2020; **35**(12): 2305-6.

103. Kolanu N, Silverstone EJ, Ho BH, et al. Clinical Utility of Computer-Aided Diagnosis of Vertebral Fractures From Computed Tomography Images. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2020; **35**(12): 2307-12.

104. Howlett DC, Drinkwater KJ, Mahmood N, Illes J, Griffin J, Javaid K. Radiology reporting of osteoporotic vertebral fragility fractures on computed tomography studies: results of a UK national audit. Eur Radiol 2020; **30**(9): 4713-23.

105. Kim YM, Demissie S, Genant HK, et al. Identification of prevalent vertebral fractures using CT lateral scout views: a comparison of semi-automated quantitative vertebral morphometry and radiologist semi-quantitative grading. Osteoporos Int 2012; **23**(3): 1007-16.

106. Rubin KH, Rothmann MJ, Holmberg T, et al. Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. Osteoporos Int 2018; **29**(3): 567-78.

107. Merlijn T, Swart KM, van Schoor NM, et al. The Effect of a Screening and Treatment Program for the Prevention of Fractures in Older Women: A Randomized Pragmatic Trial. J Bone Miner Res 2019; **34**(11): 1993-2000.

108. Merlijn T, Swart KMA, van der Horst HE, Netelenbos JC, Elders PJM. Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis. Osteoporos Int 2020; **31**(2): 251-7.

109. Ismail AA, Cooper C, Felsenberg D, et al. Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. European Vertebral Osteoporosis Study Group. Osteoporos Int 1999; **9**(3): 206-13.

110. Zhang Q, Dong J, Zhou D, Liu F. Comparative risk of fracture for bariatric procedures in patients with obesity: A systematic review and Bayesian network meta-analysis. International journal of surgery (London, England) 2020; **75**: 13-23.

111. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. Osteoporos Int 2008; **19**(10): 1395-408.

112. National Institute for Health and Care Excellence. Bisphosphonates for treating osteoporosis. Technology appraisal guidance [TA464]. **https://www.nice.org.uk/guidance/ta464**, 2019.

113. McCloskey E, Kanis JA, Johansson H, et al. FRAX-based assessment and intervention thresholds--an exploration of thresholds in women aged 50 years and older in the UK. Osteoporos Int 2015; **26**(8): 2091-9.

114. Shepstone L, Lenaghan E, Cooper C, et al. Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. Lancet 2018; **391**(10122): 741-7.

115. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med 2016; **375**(16): 1532-43.

116. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med 2017; **377**(15): 1417-27.

117. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2018; **391**(10117): 230-40.

118. Kanis JA, Harvey NC, McCloskey E, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int 2020; **31**(1): 1-12.

119. Delmas PD, Genant HK, Crans GG, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone 2003; **33**(4): 522-32.

120. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019; **30**(1): 3-44.

121. Johnell O, Oden A, Caulin F, Kanis JA. Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. Osteoporos Int 2001; **12**(3): 207-14.

122. Giangregorio LM, Leslie WD. Time since prior fracture is a risk modifier for 10-year osteoporotic fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2010; **25**(6): 1400-5.

123. Dretakis KE, Dretakis EK, Papakitsou EF, Psarakis S, Steriopoulos K. Possible Predisposing Factors for the Second Hip Fracture. Calcified Tissue International 1998; **62**(4): 366-9.

124. Nymark T, Lauritsen JM, Ovesen O, Röck ND, Jeune B. Short time-frame from first to second hip fracture in the Funen County Hip Fracture Study. Osteoporos Int 2006; **17**(9): 1353-7.

125. Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2009; **24**(7): 1299-307.

126. van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 2009; **68**(1): 99-102.

127. Johansson H, Siggeirsdóttir K, Harvey NC, et al. Imminent risk of fracture after fracture. Osteoporos Int 2017; **28**(3): 775-80.

128. Kanis JA, Johansson H, Harvey NC, et al. The effect on subsequent fracture risk of age, sex, and prior fracture site by recency of prior fracture. Osteoporosis International 2021.

129. Body JJ, Marin F, Kendler DL, et al. Efficacy of teriparatide compared with risedronate on FRAX(®)-defined major osteoporotic fractures: results of the VERO clinical trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2020; **31**(10): 1935-42.

130. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007; **357**(18): 1799-809.

131. Kanis JA, Johansson H, Harvey NC, et al. An assessment of intervention thresholds for very high fracture risk applied to the NOGG guidelines. Osteoporos Int 2021: 10.1007/s00198-021-5942-2.

132. Kanis JA, Rizzoli R, Cooper C, Reginster JY. Challenges for the development of bone-forming agents in Europe. Calcif Tissue Int 2014; **94**(5): 469-73.

133. Johansson H, Kanis JA, Oden A, Compston J, McCloskey E. A comparison of case-finding strategies in the UK for the management of hip fractures. Osteoporos Int 2012; **23**(3): 907-15.

134. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; **280**(24): 2077-82.

135. Eastell R, Black DM, Boonen S, et al. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. J Clin Endocrinol Metab, 2009; **94**(9): 3215-25.

136. Harvey NC, Kanis JA, Odén A, et al. Efficacy of weekly teriparatide does not vary by baseline fracture probability calculated using FRAX. Osteoporos Int 2015; **26**(9): 2347-53.

137. McCloskey E. A BMD threshold for treatment efficacy in osteoporosis? A need to consider the whole evidence base. Osteoporos Int 2016; **27**(1): 417-9.

138. Reid IR, Horne AM, Mihov B, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. N Engl J Med, 2018; **379**(25): 2407-16.

139. Johansson H, Oden A, Johnell O, et al. Optimization of BMD measurements to identify high risk groups for treatment--a test analysis. J Bone Mineral Res 2004; **19**(6): 906-13.

140. Leslie WD, Majumdar SR, Lix LM, et al. High fracture probability with FRAX usually indicates densitometric osteoporosis: implications for clinical practice. Osteoporos Int 2012; **23**(1): 391-7.

141. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Mineral Research; 2012; **27**(6): 1243-51.

142. Fabiani R, Naldini G, Chiavarini M. Dietary Patterns in Relation to Low Bone Mineral Density and Fracture Risk: A Systematic Review and Meta-Analysis. Advances in nutrition (Bethesda, Md) 2019; **10**(2): 219-36.

143. Lin P-H, Ginty F, Appel LJ, et al. The DASH Diet and Sodium Reduction Improve Markers of Bone Turnover and Calcium Metabolism in Adults. The Journal of Nutrition 2003; **133**(10): 3130-6.

144. Groenendijk I, den Boeft L, van Loon LJC, de Groot L. High Versus low Dietary Protein Intake and Bone Health in Older Adults: a Systematic Review and Meta-Analysis. Computational and structural biotechnology journal 2019; **17**: 1101-12.

145. Darling AL, Manders RJF, Sahni S, et al. Dietary protein and bone health across the life-course: an updated systematic review and meta-analysis over 40 years. Osteoporosis International 2019; **30**(4): 741-61.

146. Myint MW, Wu J, Wong E, et al. Clinical benefits of oral nutritional supplementation for elderly hip fracture patients: a single blind randomised controlled trial. Age Ageing 2013; **42**(1): 39-45.

147. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutrition reviews 2019; **77**(1): 1-18.

148. Tong TYN, Appleby PN, Armstrong MEG, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC medicine 2020; **18**(1): 353.

149. Department of Health. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HMSO, 1991.

150. Scientific Advisory Committee on Nutrition (SACN). Vitamin D and Health. **https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition**, 2016.

151. Royal Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. **https://strwebprdmedia.blob.core.windows.net/media/ef2ideu2/ros-vitamin-d-and-bone-health-in-adults-february-2020.pdf**, 2018.

152. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA network open 2019; **2**(12): e1917789.

153. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007; **370**(9588): 657-66.

154. Group. DVDIPAoRT. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. Bmj 2010; **340**: b5463.

155. Harvey NC, Biver E, Kaufman JM, et al. The role of calcium supplementation in healthy musculoskeletal ageing. Osteoporosis International 2017; **28**(2): 447-62.

156. Kahwati LC, Weber RP, Pan H, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2018; **319**(15): 1600-12.

157. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010; **303**(18): 1815-22.

158. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA internal medicine 2016; **176**(2): 175-83.

159. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev 2011; (7): Cd000333.

160. Kemmler W, Shojaa M, Kohl M, von Stengel S. Effects of Different Types of Exercise on Bone Mineral Density in Postmenopausal Women: A Systematic Review and Meta-analysis. Calcif Tissue Int 2020; **107**(5): 409-39.

161. Babatunde OO, Bourton AL, Hind K, Paskins Z, Forsyth JJ. Exercise Interventions for Preventing and Treating Low Bone Mass in the Forearm: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil 2020; **101**(3): 487-511.

162. Kelley GA, Kelley KS, Kohrt WM. Exercise and bone mineral density in men: a meta-analysis of randomized controlled trials. Bone 2013; **53**(1): 103-11.

163. Royal Osteoporosis Society. Strong, Steady and Straight; An Expert Consensus Statement on physical activity and exercise for osteoporosis. **https://theros.org.uk/media/0o5h1l53/ros-strong-steady-straight-quick-guide-february-2019.pdf**, 2018.

164. Kunutsor SK, Leyland S, Skelton DA, et al. Adverse events and safety issues associated with physical activity and exercise for adults with osteoporosis and osteopenia: A systematic review of observational studies and an updated review of interventional studies. Journal of frailty, sarcopenia and falls 2018; **3**(4): 155-78.

165. Bhasin S, Gill TM, Reuben DB, et al. A Randomized Trial of a Multifactorial Strategy to Prevent Serious Fall Injuries. N Engl J Med 2020; **383**(2): 129-40.

166. Lamb SE, Bruce J, Hossain A, et al. Screening and Intervention to Prevent Falls and Fractures in Older People. N Engl J Med 2020; **383**(19): 1848-59.

167. El-Khoury F, Cassou B, Charles M-A, Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. 2013; **347**: f6234.

168. Sherrington C, Fairhall NJ, Wallbank GK, et al. Exercise for preventing falls in older people living in the community. Cochrane Database Syst Rev 2019; **1**(1): Cd012424.

169. Zhao R, Bu W, Chen X. The efficacy and safety of exercise for prevention of fall-related injuries in older people with different health conditions, and differing intervention protocols: a meta-analysis of randomized controlled trials. BMC Geriatr 2019; **19**(1): 341.

170. Sherrington C, Michaleff ZA, Fairhall N, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. British journal of sports medicine 2017; **51**(24): 1750-8.

171. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012; (9): Cd007146.

172. Jepsen DB, Thomsen K, Hansen S, Jørgensen NR, Masud T, Ryg J. Effect of whole-body vibration exercise in preventing falls and fractures: a systematic review and meta-analysis. BMJ Open 2017; **7**(12): e018342.

173. Thorin MH, Wihlborg A, Åkesson K, Gerdhem P. Smoking, smoking cessation, and fracture risk in elderly women followed for 10 years. Osteoporos Int 2016; **27**(1): 249-55.

174. Shen GS, Li Y, Zhao G, et al. Cigarette smoking and risk of hip fracture in women: a meta-analysis of prospective cohort studies. Injury 2015; **46**(7): 1333-40.

175. Wei Min, Rongze An, Songjun Li, Jiaying Feng, Jin Yang, Huang. Z. The effects of preoperative smoking cessation on the healing of fractures and postoperative complications: A systematic review and meta-analysis. Biomedical Research 2017; **28**: 1883-9.

176. Song TH, Shim JC, Jung DU, et al. Increased Bone Mineral Density after Abstinence in Male Patients with Alcohol Dependence. Clin Psychopharmacol Neurosci 2018; **16**(3): 282-9.

177. Health. Do. UK Chief Medical Officers' Alcohol Guidelines Review Summary of the proposed new guidelines. Williams Lea, 2016.

178. Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med 2014; **161**(10): 711-23.

179. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; **348**(9041): 1535-41.

180. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000; **343**(9): 604-10.

181. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 1998; **339**(5): 292-9.

182. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999; **282**(14): 1344-52.

183. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; **11**(1): 83-91.

184. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res 2009; **24**(4): 719-25.

185. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000; **67**(4): 277-85.

186. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 2000; **15**(6): 1006-13.

187. Delmas PD, Recker RR, Chesnut CH, 3rd, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int 2004; **15**(10): 792-8.

188. Chesnut CH, 3rd, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004; **19**(8): 1241-9.

189. Reginster JY, Adami S, Lakatos P, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006; **65**(5): 654-61.

190. Eisman JA, Civitelli R, Adami S, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol 2008; **35**(3): 488-97.

191. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; **356**(18): 1809-22.

192. Boonen S, Reginster JY, Kaufman JM, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med 2012; **367**(18): 1714-23.

193. Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009; **373**(9671): 1253-63.

194. Reid IR, Horne AM, Mihov B, et al. Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women. J Bone Miner Res 2020; **35**(1): 20-7.

195. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 2010; **95**(9): 4380-7.

196. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. Lancet Diabetes Endocrinol 2018; **6**(6): 445-54.

197. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; **361**(8): 756-65.

198. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. The lancet Diabetes & endocrinology 2017; **5**(7): 513-23.

199. Langdahl BL, Teglbjaerg CS, Ho PR, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab 2015; **100**(4): 1335-42.

200. 2014. **https://www.gov.uk/drug-safety-update/denosumab-monitoring-recommended** (accessed January 7th 2021).

201. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. The Journal of clinical endocrinology and metabolism 2011; **96**(4): 972-80.

202. Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. The Journal of clinical endocrinology and metabolism 2011; **96**(2): 394-402.

203. Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. The Journal of clinical endocrinology and metabolism 2020.

204. Cummings SR, Ferrari S, Eastell R, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res; 2018; **33**(2): 190-8.

205. Dennison EM, Cooper C, Kanis JA, et al. Fracture risk following intermission of osteoporosis therapy. Osteoporos Int 2019; **30**(9): 1733-43.

206. Reid IR, Horne AM, Mihov B, Gamble GD. Bone Loss After Denosumab: Only Partial Protection with Zoledronate. Calcif Tissue Int 2017; **101**(4): 371-4.

207. Horne AM, Mihov B, Reid IR. Effect of Zoledronate on Bone Loss After Romosozumab/Denosumab: 2-Year Follow-up. Calcif Tissue Int 2019; **105**(1): 107-8.

208. Anastasilakis AD, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Makras P. Zoledronate for the Prevention of Bone Loss in Women Discontinuing Denosumab Treatment. A Prospective 2-Year Clinical Trial. J Bone Mineral Res; 2019; **34**(12): 2220-8.

209. Everts-Graber J, Reichenbach S, Ziswiler HR, Studer U, Lehmann T. A Single Infusion of Zoledronate in Postmenopausal Women Following Denosumab Discontinuation Results in Partial Conservation of Bone Mass Gains. J Bone Miner Res: 2020; **35**(7): 1207-15.

210. Sølling AS, Harsløf T, Langdahl B. Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial. J Bone Mineral Research 2020; **35**(10): 1858-70.

211. Makras P, Appelman-Dijkstra NM, Papapoulos SE, et al. The Duration of Denosumab Treatment and the Efficacy of Zoledronate to Preserve Bone Mineral Density After Its Discontinuation. The Journal of clinical endocrinology and metabolism 2021; **106**(10): e4155-e62.

212. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone 2017; **105**: 11-7.

213. Kendler D, Chines A, Clark P, et al. Bone Mineral Density After Transitioning From Denosumab to Alendronate. J Clin Endocrinol Metab, 2020; **105**(3): e255-64.

214. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012; (7): CD004143.

215. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; **288**(3): 321-33.

216. Gartlehner G, Patel SV, Feltner C, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2017; **318**(22): 2234-49.

217. Rozenberg S, Al-Daghri N, Aubertin-Leheudre M, et al. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporos Int 2020; **31**(12): 2271-86.

218. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. Ann Intern Med 1990; **113**(9): 649-55.

219. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; **282**(7): 637-45.

220. Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the framingham stroke risk score. Am J Med 2009; **122**(8): 754-61.

221. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; **355**(2): 125-37.

222. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; **350**(5): 459-68.

223. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; **90**(5): 2816-22.

224. Kaufman JM, Audran M, Bianchi G, et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 2013; **98**(2): 592-601.

225. Osborne V, Layton D, Perrio M, Wilton L, Shakir SA. Incidence of venous thromboembolism in users of strontium ranelate: an analysis of data from a prescription-event monitoring study in England. Drug Saf 2010; **33**(7): 579-91.

226. Agency EM. PSUR assessment report Strontium Ranelate. 2013.

227. Blake GM, Compston JE, Fogelman I. Could strontium ranelate have a synergistic role in the treatment of osteoporosis? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2009; **24**(8): 1354-7.

228. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; **344**(19): 1434-41.

229. Diez-Perez A, Marin F, Eriksen EF, Kendler DL, Krege JH, Delgado-Rodriguez M. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: A systematic review and meta-analysis. Bone 2019; **120**: 1-8.

230. Simpson EL, Martyn-St James M, Hamilton J, et al. Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: A systematic review and network meta-analysis. Bone 2020; **130**: 115081.

231. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 2003; **18**(1): 9-17.

232. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 2009; **60**(11): 3346-55.

233. Kendler DL, Bone HG, Massari F, et al. Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab. Osteoporos Int 2019; **30**(12): 2437-48.

234. Rittmaster RS, Bolognese M, Ettinger MP, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. J Clin Endocrinol Metab; 2000; **85**(6): 2129-34.

235. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015; **386**(9999): 1147-55.

236. Cosman F, Crittenden DB, Ferrari S, et al. FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab. J Bone Mineral Res: 2018; **33**(7): 1219-26.

237. McClung MR, Brown JP, Diez-Perez A, et al. Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study. J Bone Miner Res 2018; **33**(8): 1397-406.

238. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One Year of Romosozumab Followed by Two Years of Denosumab Maintains Fracture Risk Reductions: Results of the FRAME Extension Study. J Bone Miner Research, 2019; **34**(3): 419-28.

239. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet 2017; **390**(10102): 1585-94.

240. Keaveny TM, Crittenden DB, Bolognese MA, et al. Greater Gains in Spine and Hip Strength for Romosozumab Compared With Teriparatide in Postmenopausal Women With Low Bone Mass. J Bone Miner Research; 2017; **32**(9): 1956-62.

241. Ebina K, Hirao M, Tsuboi H, et al. Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis. Bone 2020; **140**: 115574.

242. Nayak S, Greenspan SL. A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. Osteoporos Int 2019; **30**(4): 705-20.

243. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. NICE guideline [NG56]. **https://www.nice.org.uk/guidance/ng56**, 2016.

244. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Research: 2016; **31**(1): 16-35.

245. Fink HA, MacDonald R, Forte ML, et al. Long-Term Drug Therapy and Drug Discontinuations and Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Ann Intern Med 2019; **171**(1): 37-50.

246. Ensrud KE, Barrett-Connor EL, Schwartz A, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Min Res, 2004; **19**(8): 1259-69.

247. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. Jama 2006; **296**(24): 2927-38.

248. Ravn P, Christensen JO, Baumann M, Clemmesen B. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. Bone 1998; **22**(5): 559-64.

249. Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int 2008; **19**(3): 365-72.

250. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Mineral Research 2012; **27**(2): 243-54.

251. Kim TY, Bauer DC, McNabb BL, et al. Comparison of BMD Changes and Bone Formation Marker Levels 3 Years After Bisphosphonate Discontinuation: FLEX and HORIZON-PFT Extension I Trials. J Bone Mineral Research, 2019; **34**(5): 810-6.

252. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA internal medicine 2014; **174**(7): 1126-34.

253. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus. Journal of Bone and Mineral Research 2015; **30**(1): 3-23.

254. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research 2007; **22**(10): 1479-91.

255. Scottish Dental Clinical Effectiveness Programme. Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw: Dental Clinical Guidance. **https://www.sdcep.org.uk/wp-content/uploads/2017/04/SDCEP-Oral-Health-Management-of-Patients-at-Risk-of-MRONJ-Guidance-full.pdf**, 2017.

256. Salzman R, Hoza J, Perina V, Stárek I. Osteonecrosis of the external auditory canal associated with oral bisphosphonate therapy: case report and literature review. Otol Neurotol 2013; **34**(2): 209-13.

257. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical Femur Fractures: Review of Epidemiology, Relationship to Bisphosphonates, Prevention, and Clinical Management. Endocr Rev 2019; **40**(2): 333-68.

258. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Min Research 2010; **25**(11): 2267-94.

259. Shane E, Burr D, Abrahamsen B, et al. Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research 2014; **29**(1): 1-23.

260. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. J Bone Min Research, 2013; **28**(8): 1729-37.

261. Abrahamsen B, Eiken P, Prieto-Alhambra D, Eastell R. Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study. Bmj 2016; **353**: i3365.

262. van de Laarschot DM, McKenna MJ, Abrahamsen B, et al. Medical Management of Patients After Atypical Femur Fractures: a Systematic Review and Recommendations From the European Calcified Tissue Society. J Clin Endocrin Metab 2020; **105**(5): 1682-99.

263. Carter M. Prevention of Glucocorticoid-Induced Osteoporosis: Clinical audit to evaluate the implementation of National Osteoporosis Guideline Group 2017 guidelines in a primary care setting. J Clin Densitom 2019; **22**(1): 25-30.

264. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002; **13**(10): 777-87.

265. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001; **44**(1): 202-11.

266. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999; **42**(11): 2309-18.

267. Deng J, Silver Z, Huang E, et al. Pharmacological prevention of fractures in patients undergoing glucocorticoid therapies: a systematic review and network meta-analysis. Rheumatology (Oxford) 2020.

268. Brown JE, Handforth C, Compston JE, et al. Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group. J Bone Oncol 2020; **25**: 100311.

269. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; **97**(6): 1802-22.

270. Health NIf. Osteoporosis in Men. 2018.

271. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 2002; **87**(8): 3656-61.

272. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005; **352**(2): 154-64.

273. Joseph JS, Lam V, Patel MI. Preventing Osteoporosis in Men Taking Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-Analysis. Eur Urol Oncol 2019; **2**(5): 551-61.

274. Poon Y, Pechlivanoglou P, Alibhai SMH, et al. Systematic review and network meta-analysis on the relative efficacy of osteoporotic medications: men with prostate cancer on continuous androgen-deprivation therapy to reduce risk of fragility fractures. BJU Int 2018; **121**(1): 17-28.

275. Reid DM, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev 2008; **34 Suppl 1**: S3-18.

276. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol 2017; **7**: 1-12.

277. Excellence NIfHaC. Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates. 2017.

278. Waqas K, Lima Ferreira J, Tsourdi E, Body JJ, Hadji P, Zillikens MC. Updated guidance on the management of cancer treatment-induced bone loss (CTIBL) in pre- and postmenopausal women with early-stage breast cancer. J Bone Oncol 2021; **28**: 100355.

279. Miyashita H, Satoi S, Kuno T, Cruz C, Malamud S, Kim SM. Bone modifying agents for bone loss in patients with aromatase inhibitor as adjuvant treatment for breast cancer; insights from a network meta-analysis. Breast Cancer Res Treat 2020; **181**(2): 279-89.

280. World Health Organization. Traitement de la douleur cancéreuse. Genève: Organisation mondiale de la Santé. https://apps.who.int/iris/handle/10665/41712, 1987.

281. Schofield P. The Assessment of Pain in Older People: UK National Guidelines. Age and Ageing 2018; **47**(suppl_1): i1-i22.

282. British Geriatric Society. Guidance on the management of pain in older people. Age and Ageing 2013; **42**(suppl_1): i1-i57.

283. Knopp-Sihota JA, Newburn-Cook CV, Homik J, Cummings GG, Voaklander D. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Osteoporos Int 2012; **23**(1): 17-38.

284. European Medicines Agency. European Medicines Agency recommends limiting long-term use of calcitonin medicines. **https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-limiting-long-term-use-calcitonin-medicines**, 2012.

285. Armingeat T, Brondino R, Pham T, Legré V, Lafforgue P. Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. Osteoporos Int 2006; **17**(11): 1659-65.

286. Gibbs JC, MacIntyre NJ, Ponzano M, et al. Exercise for improving outcomes after osteoporotic vertebral fracture. Cochrane Database of Systematic Reviews 2019; (7).

287. Ebeling PR, Akesson K, Bauer DC, et al. The Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report. 2019; **34**(1): 3-21.

288. Svensson HK, Olsson LE, Hansson T, Karlsson J, Hansson-Olofsson E. The effects of person-centered or other supportive interventions in older women with osteoporotic vertebral compression fractures-a systematic review of the literature. Osteoporos Int 2017; **28**(9): 2521-40.

289. Hofler RC, Jones GA. Bracing for Acute and Subacute Osteoporotic Compression Fractures: A Systematic Review of the Literature. World neurosurgery 2020; **141**: e453-e60.

290. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev 2018; **11**(11): Cd006349.

291. Zambito A, Bianchini D, Gatti D, Rossini M, Adami S, Viapiana O. Interferential and horizontal therapies in chronic low back pain due to multiple vertebral fractures: a randomized, double blind, clinical study. Osteoporosis International 2007; **18**(11): 1541-5.

292. Axelsson KF, Johansson H, Lundh D, Möller M, Lorentzon M. Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study. J Bone Miner Res 2020; **35**(7): 1216-23.

293. Wu CH, Tu ST, Chang YF, et al. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. Bone 2018; **111**: 92-100.

294. Department of Health. Fracture prevention services - an economic evaluation. 2009.

295. NHS_RightCare. Falls and Fragility Fractures Pathway. **https://www.england.nhs.uk/rightcare/products/pathways/falls-and-fragility-fractures-pathway/**, 2017.

296. Javaid MK, Kyer C, Mitchell PJ, et al. Effective secondary fracture prevention: implementation of a global benchmarking of clinical quality using the IOF Capture the Fracture(R) Best Practice Framework tool. Osteoporos Int 2015; **26**(11): 2573-8.

297. Royal Osteoporosis Society. Effective Secondary Prevention of Fragility Fractures: Clinical Standards for Fracture Liaison Services **https://theros.org.uk/media/1eubz33w/ros-clinical-standards-for-fracture-liaison-services-august-2019.pdf**, 2019.

298. Ganda K, Puech M, Chen J. S, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporosis International 2013; **24**(2): 393-406.

299. Ganda K, Mitchell PJ, Seibel MJ. Chapter 3, Models of Secondary Fracture Prevention: Systematic review and Metaanalysis of Outcomes. In: Mitchell PJ, Seibel MJ, eds. Secondary Fracture Prevention, an International Perspective: Elsevier Inc; 2019: 33-62.

300. Wu CH, Chen CH, Chen PH, et al. Identifying characteristics of an effective fracture liaison service: systematic literature review. Osteoporos Int 2018; **29**(5): 1023-47.

301. Public Health England. Falls and fracture consensus statement: Supporting commissioning for prevention **www.gov.uk/phe**, 2017.

302. Royal Osteoporosis Society. Clinical Guidance for the Effective Identification of Vertebral Fractures **https://theros.org.uk/healthcare-professionals/tools-and-resources/clinical-guidance/**, 2017.

303. Laurna Bullock, Fay Crawford-Manning, Elizabeth Cottrell, et al. Co-designing a model Fracture Liaison Service consultation with patients, carers and clinicians: a Delphi survey to inform the content of the i-FraP complex consultation intervention. Archives in Osteoporosis 2021; **in press**.

304. Paskins Z, Torres Roldan VD, Hawarden AW, et al. Quality and effectiveness of osteoporosis treatment decision aids: a systematic review and environmental scan. Osteoporos Int 2020.

305. National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical Guideline [CG76]. **https://www.nice.org.uk/guidance/cg76**, 2009.

306. Cornelissen D, de Kunder S, Si L, et al. Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review. Osteoporos Int 2020; **31**(9): 1645-69.

307. Martin J, Viprey M, Castagne B, et al. Interventions to improve osteoporosis care: a systematic review and meta-analysis. Osteoporos Int 2020; **31**(3): 429-46.

308. Clynes MA, Westbury LD, Dennison EM, et al. Bone densitometry worldwide: a global survey by the ISCD and IOF. Osteoporos Int 2020; **31**(9): 1779-86.

309. Foundation TH. Quality improvement made simple: What everyone should know about health care quality improvement. The Health Foundation, 8 Salisbury Square, London, 2021.

310. Javaid MK, Harvey NC, McCloskey E, Kanis JA, C C. Assessment and management of imminent fracture risk in the setting of the fracture liaison service. Osteo Internat 2021; **in press**.

311. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013; **66**(7): 719-25.

312. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. 2008; **337**: a744.

313. National Institute for Health and Care Excellence. The guidelines manual. Process and methods [PMG6]. Section 9 Developing and wording guideline recommendations, 2012.

314. Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. J Am Geriatr Soc 2017; **65**(3): 490-5.

315. Zeng LF, Pan BQ, Liang GH, et al. Does Routine Anti-Osteoporosis Medication Lower the Risk of Fractures in Male Subjects? An Updated Systematic Review With Meta-Analysis of Clinical Trials. Frontiers in pharmacology 2019; **10**: 882.

316. Wang YK, Zhang YM, Qin SQ, et al. Effects of alendronate for treatment of glucocorticoid-induced osteoporosis: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018; **97**(42): e12691.

317. Yanbeiy ZA, Hansen KE. Denosumab in the treatment of glucocorticoid-induced osteoporosis: a systematic review and meta-analysis. Drug Des Devel Ther 2019; **13**: 2843-52.