UK consensus guideline on the management of patients at low, high, and very high risk of osteoporotic fracture

Guidelines

summarising clinical guidelines for primary care

Guidelines identified a need for clinical guidance in a specific area and approached UCB Pharma Ltd for an educational grant to support the development of a working party guideline. This working party guideline was developed by *Guidelines*, and the Chairs and members of the group were chosen by and convened by *Guidelines*. The content is independent of and not influenced by UCB Pharma Ltd, who checked the final document for technical accuracy and to ensure compliance with regulations.

August 2020

UK consensus guideline on the management of patients at low, high, and very high risk of osteoporotic fracture

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Introduction

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, increasing bone fragility and susceptibility to fracture.[1,2] This condition can lead to fragility fractures, where bones break easily after falls from standing height or less.[1,3] Diagnosis of osteoporosis is confirmed using dual-energy X-ray absorptiometry scans that measure bone mineral density (BMD). The difference between the person's BMD and that of the average value in young adult women is shown by the T-score. People with a T-score that is 2.5 standard deviations or more below the young adult mean value for women are diagnosed with osteoporosis, and if in addition to this there are one or more documented fragility fractures they are diagnosed with severe or established osteoporosis.[2] This definition for osteoporosis using the T-score is also used for diagnosing men and patients in different ethnic groups. However, some patients can be diagnosed with osteoporosis without the need for measurement of BMD, for example, after specific fragility fractures and by age.

In the UK, more than 3 million people are estimated to have osteoporosis.[3] Reduced bone density is the major risk factor for fragility fracture, but other factors also increase the risk (Box 1). Increasing age in both sexes and menopause in women leads to increased bone loss, and therefore the prevalence of osteoporosis increases markedly with age—for example, in women it increases from 2% at 50 years of age to >25% at 80 years of age.[1] An estimated 500,000 fragility fractures occur annually, which impact people in many ways, leading to social isolation, loss of independence, disability, long-term pain, and premature death.[3]

In 2019, Kanis et al published an algorithm for the management of patients at low, high, and very high risk of osteoporotic fractures based on the FRAX risk assessment tool.[4] A study has demonstrated that FRAX and other fracture risk prediction tools may underestimate fracture risk in the first two years post fracture, the imminent fracture period.[5,6] Hence, the need to incorporate the recency of fracture with scores for fracture risk at an individual level.[4] This working party guideline covers the management of patients at low, high, and very high risk of osteoporotic fracture and is intended for healthcare professionals who interact with these patients.

Box 1: Risk factors for fragility fractures[1]

- Previous fragility fracture
- Current or frequent recent use of oral or systemic glucocorticoids
- Increasing age
- Female sex/menopause
- Causes of secondary osteoporosis
- Low body mass index (<18.5 kg/m^2)
- History of falls
- Parental history of hip fracture
- Smoking
- Alcohol intake >14 units per week.

Treatment of osteoporosis

Preventative treatment given as soon as possible after a fragility fracture will reduce the number of subsequent fractures and morbidity compared with delayed treatment.[4] Various therapies and treatments are available to prevent fragility fractures in people at risk.[1] Lifestyle modifications provide a non-pharmacological approach for all patients with osteoporosis and are the first option for those at lowest risk (Box 2). Specific evidence-based physical activities and exercises can strengthen bones, reduce falls, and reduce the risk of vertebral fracture as well as manage symptoms of vertebral fracture,[7,8] but patients do not always receive sufficient information around non-pharmacological management of osteoporosis.[9] Pharmacological treatments for those at higher risk fall into two categories—antiresorptive agents and bone-forming (anabolic) agents (Box 3).

The antiresorptive agents include bisphosphonates (alendronate, risedronate, ibandronic acid, and zoledronic acid), the selective oestrogen receptor modulator (SERM) raloxifene, hormone replacement therapy, and the receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor denosumab.[10–17] The bisphosphonates inhibit osteoclast-mediated bone turnover

Box 2: Lifestyle modifications to improve bone health

- Recommend for all patients irrespective of risk
- Modifications include:[2]
  - exercise
  - diet, including adequate calcium/vitamin D intake
  - reducing the risk of falls
  - stopping smoking
  - reducing alcohol intake to ≤2 units/day
- Tailor recommendations to each patient's own circumstances and comorbidities
- All patients with osteoporosis should exercise using 'strong, steady, and straight' guidance to:[7,8]
  - promote bone strength
  - improve balance and muscle strength to reduce falls and resulting fractures
  - care for the spine by keeping the back straight to reduce the risk of vertebral fracture, and improve posture and relieve pain after vertebral fracture.

Box 3: Drugs available to treat osteoporosis[A]

- Antiresorptive[10–17]
  - bisphosphonates:
    - alendronate
    - risedronate
    - ibandronic acid (oral or injection)
    - zoledronic acid (IV)
  - raloxifene (in women only)
  - denosumab (injection)
  - hormone replacement therapy (menopausal women/testosterone replacement in male hypogonadism)
- Bone forming (anabolic)[18–21]
  - teriparatide (self-injected)
  - biosimilar teriparatide (self-injected)
  - romosozumab (injection).

[A] Prescribers should refer to the individual summaries of product characteristics.[10–15,18–21]

IV=intravenous

(resorption).[10–13] Raloxifene acts as an agonist on bone, and, in postmenopausal women with osteoporosis, raloxifene reduces the incidence of vertebral fractures, preserves bone mass, and increases BMD.[14] Denosumab is a human monoclonal antibody that targets and binds to RANKL—a transmembrane or soluble protein essential for formation, function, and survival of osteoclasts, which are responsible for bone resorption.[15] Denosumab prevents the RANKL/RANK interaction from occurring, reducing osteoclast numbers and function, and decreasing bone resorption. Menopausal hormone therapy is the first line treatment for premature ovarian insufficiency; it is also prescribed in perimenopause and postmenopause for symptomatic relief as well as bone protection.[17] Alendronate, risedronate, ibandronic acid, raloxifene, menopausal hormone therapy, and denosumab are usually prescribed in general practice. Zoledronic acid is usually prescribed and delivered in the hospital setting although in some sites community delivery is being tested.

The bone-forming agents comprise teriparatide, biosimilar teriparatide, and romosozumab. Teriparatide—the first bone anabolic agent—is the active fragment of endogenous human parathyroid hormone (PTH).[18,22] PTH stimulates bone formation by directly affecting bone-forming cells (osteoblasts).[18] Biosimilars of teriparatide are also licensed for patients with osteoporosis.[19,20] Romosozumab is a humanised monoclonal antibody (IgG2) that binds and inhibits sclerostin, increasing bone formation due to the activation of bone lining cells, increasing bone matrix production by osteoblasts, and recruiting osteoprogenitor cells.[21] It also results in changes to the expression of osteoclast mediators, which decreases bone resorption.[21] This dual effect results in rapid increases in trabecular and cortical bone mass, improvements in bone structure, and strength.[21] All bone-forming agents are reserved for use in specialist services, they are not usually recommended as first-line therapies by NICE. Teriparatide and biosimilar teriparatide may be used for a course of 24 months, which may not be repeated, while romosozumab may be used for 12 months; after these treatment courses, patients should be switched to antiresorptive agents.[18–21]

Strontium ranelate is another agent that is licensed in the NHS but its use is limited due to increased risk of venous thromboembolic and cardiovascular events.[23]

Risk assessment

Risk assessment is vital so that anti-osteoporosis medication (AOM) can be started as early as possible.[4] Current NICE guidance recommends two risk assessment tools to predict the probability of a future fragility fracture—FRAX and QFracture.[1] The Scottish Intercollegiate Guidelines Network (SIGN) recommends fracture risk assessment preferably using QFracture.[23] The online FRAX risk-assessment tool allows calculation of the 10-year absolute risk of hip fracture and other major osteoporotic fractures (clinical spine, forearm, hip, or shoulder fracture), and is based on age, gender, body mass index (BMI), the presence or absence of a previous fracture, parental hip fracture, current smoking status, current use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and consumption of three or more units of alcohol per day.[23,24] While the initial FRAX assessment does not have to include measurement of BMD, a strength of the tool is that BMD measurements can be included in the assessment if available and input into the National Osteoporosis Guideline Group (NOGG) tool to indicate when AOM should be considered.[2,23,24,25] QFracture is also an online fracture risk scoring tool that can be used to predict the absolute risk of hip fracture and of major osteoporotic fractures (spine, wrist, hip, or shoulder) over 1–10 years.[23,26]

Both NICE and SIGN advise GPs not to routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.[1,23] NICE recommends assessing fracture risk in all women aged ≥65 years and men

aged ≥75 years, as well as younger women and men who have risk factors (see Box 1).[1] SIGN recommends fracture risk assessment, preferably using Qfracture, prior to measuring BMD in patients with clinical risk factors for osteoporosis and in whom AOM is being considered; they propose a 10-year fracture risk of 10% as the level at which measurement of BMD is appropriate in people who have not previously had a fragility fracture.[23] NICE recommends measurement of BMD to assess fracture risk in people younger than 40 years with a major risk factor, such as history of multiple fragility fractures, major osteoporotic fracture, or current or recent use of high-dose oral or systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).[1] The risk assessment according to FRAX or QFracture should only be used to estimate the 10-year predicted absolute fracture risk within allowed age ranges (40–90 years for FRAX and 30–99 years for QFracture);[24,26] patients older than the tools' age limits should be considered at high risk.[1]

The algorithm published by Kanis et al suggests further development of FRAX risk assessment by combining the FRAX score with BMD measurements to refine characterisation of risk by categorising patients as at low, high, or very high risk of osteoporotic fracture in order to guide treatment decisions and direct appropriate interventions.[4] In this model, an initial risk assessment uses FRAX with clinical risk factors alone to categorise patients below the lower assessment threshold (low risk), between thresholds (measure BMD and recalculate risk), and over the upper assessment threshold (very high risk). The study suggests that for patients at very high risk, treatment with an anabolic for the period allowed (12–24 months) followed by antiresorptive therapy to maintain the effect should be considered.[4] Patients who are low risk should be reassured and given advice on lifestyle, calcium/vitamin D nutrition, hormone treatment in the case of perimenopause and postmenopause in women and testosterone replacement therapy in men with male hypogonadism. Patients who fall between thresholds can be reassessed based on BMD and FRAX risk probability, including femoral neck BMD. These patients may then be reclassified; those reclassified very high or low risk are treated as described above, while those who remain in between thresholds are considered at high risk, and initial antiresorptive therapy should be considered. All patients with a prior fragility fracture are at least high risk and possibly very high risk depending on their FRAX probability.[4]

UK consensus management of patients at low, high, and very high risk of osteoporotic fracture

A working party group was convened to develop a consensus guideline and treatment algorithm to support primary care in the management of patients at low, high, and very high risk of osteoporotic fracture. Figure 1 provides an algorithm summarising the group's consensus recommendations for management of patients in these three risk groups.

Identification of patients at risk of osteoporotic fracture

- Patients at risk of osteoporotic fracture include:
  - patients with a recent (in the last 2 years) fragility fracture
    - major fractures of hip/pelvis/femur
    - distal forearm
    - vertebra
    - proximal humerus
    - rib
    - clavicle
    - tibia
  - patients identified as at risk of future fracture through opportunistic screening
  - patients at risk of future fracture due to treatments such as steroids or other bone damaging medicines.

Assessing the level of future risk

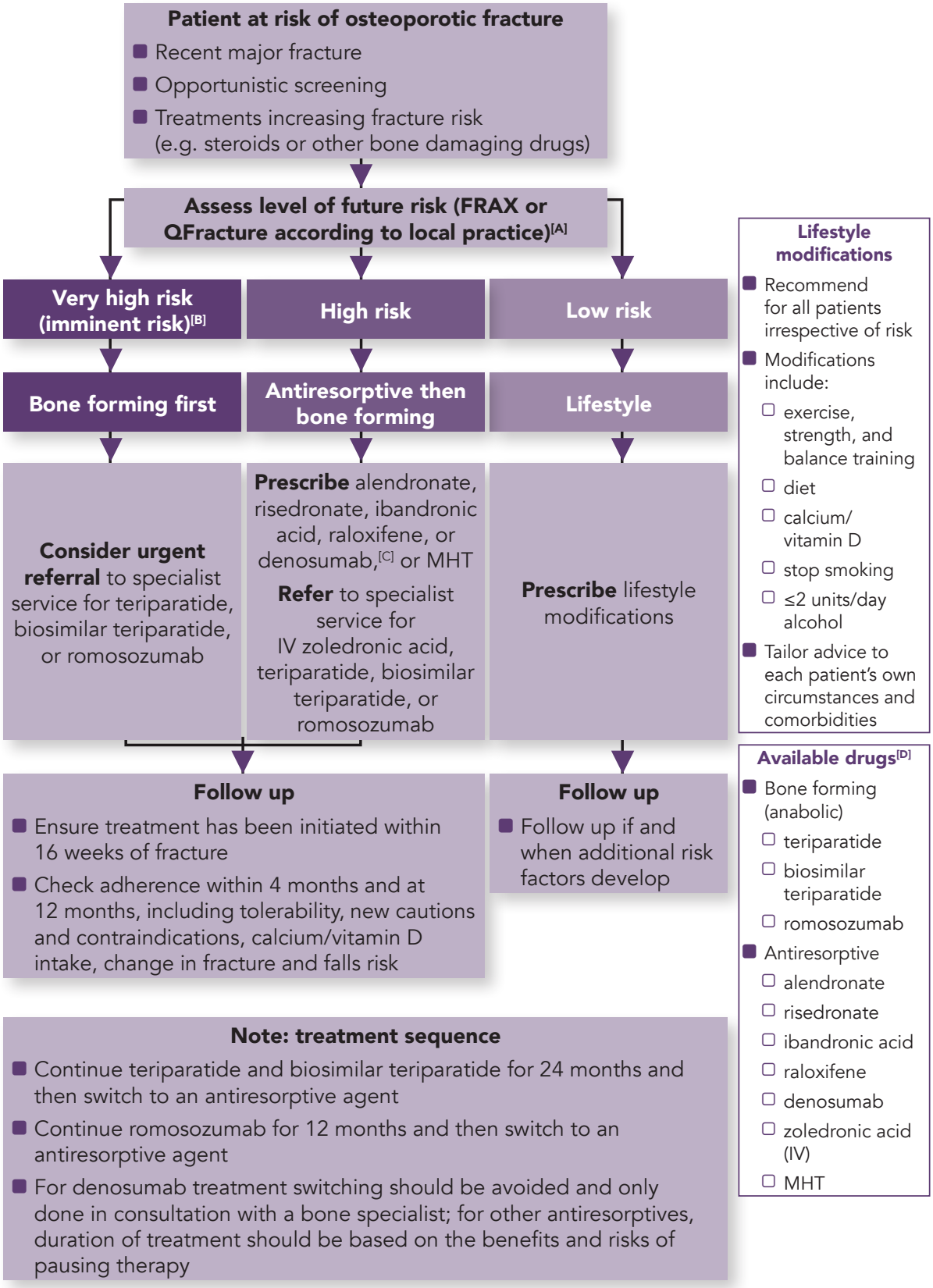
- The level of future risk should be assessed through FRAX or QFracture, according to local or national guidelines, and also take into consideration clinical features such as the site and recency of previous fractures that are not included in the risk calculation for FRAX and QFracture
  - note that FRAX but not QFracture outputs are compatible with the fracture probability nomograms in the Kanis et al algorithm[4] or NOGG guidance[2,25]
  - the SIGN guideline proposes a 10-year fracture risk of 10% as the level at which measurement of BMD is appropriate in people who have not previously had a fragility fracture and treatment should then be based on the BMD measurement[23]
  - note that the FRAX/NOGG thresholds and the SIGN recommendation are based on expert recommendation.

Managing patients based on their future risk

- Lifestyle modifications should be recommended for all patients irrespective of their level of risk (see Box 2)

- Choice of pharmacological treatment (see Box 3) varies based on the level of risk
  - the future risk of fractures is a continuum from low risk through high risk to very high risk rather than discrete risk categories
    - if a patient is close to the threshold between two levels of risk, individual patient factors should be considered when deciding on treatment options
  - good prescribing practice means that treatment in primary care often starts with a medication that has been available for some time and where the prescriber has clinical experience with the drug and any possible adverse effects
    - an individualised decision should be made for each patient based on their medical history, their level of fracture risk in the next 2 years, and the experience of the prescriber; specialists can help with treatment decisions in high risk patients, especially if the patient has previously been prescribed AOM.

Figure 1: Algorithm on the management of patients at low, high, and very high risk of osteoporotic fracture



[A] Use FRAX if using NOGG or Kanis et al 2020[4] nomograms to decide risk level. QFracture is not calibrated for these tools and decisions on treatment should be based on the BMD measurement.
[B] Imminent risk refers to a clinical setting in which a fracture has occurred within the previous 2 years.
[C] In some instances, denosumab also has to be initiated by secondary care.
[D] Prescribers should refer to the individual summaries of product characteristics.

IV=intravenous; MHT=menopausal hormone therapy; NOGG=National Osteoporosis Guideline Group

Low risk

- Patients at low risk should be reassured and require only lifestyle modifications (see Box 2)
  - provide patient information leaflets and advice on circumstances that mean they may need to seek further assessment
- Follow up if additional risk factors develop.

High risk

- Patients at high risk of future fracture should be prescribed antiresorptive agents before referral for bone-forming drugs:
  - prescribe alendronate, risedronate, ibandronic acid, raloxifene, denosumab, or hormone replacement therapy[10,11,13–17]
  - refer to specialist service for intravenous zoledronic acid, teriparatide, biosimilar teriparatide, or romosozumab[12,18–21]
- Sequence of therapy should be planned with a bone specialist unit
- Primary care follow-up:
  - ensure treatment has been initiated and advice on lifestyle modifications has been given
    - advice on lifestyle modifcations should be repeated at each consultation
  - check adherence to antiresorptive agents and whether bone-forming drugs are required in high risk patients within 4 months and at 12 months,[3,27] including:
    - tolerability
    - new cautions and contraindications
    - calcium/vitamin D intake
    - change in fracture and falls risk
  - continue to review medication and adherence annually and after 3 years assess the level of future risk through FRAX or QFracture (and measure BMD if required) according to local or national guidelines
    - practice-based pharmacists may undertake annual reviews as part of a medicines optimisation review and repeat prescribing; liaison with community pharmacists will enhance patient care.

Very high risk

- Very high (or imminent) risk is defined by a high FRAX score with a history of major fracture of the hip/pelvis/femur, vertebra, humerus, or ribs in the last 2 years[4]
- Patients at very high risk of future fracture should be prescribed bone-forming (anabolic) drugs:
  - consider urgent referral to specialist service for teriparatide, biosimilar PTH, or romosozumab;[18–21] urgent treatment will require the development of new primary and secondary care pathways

Useful resources

- FRAX tool: www.sheffield.ac.uk/FRAX/tool.aspx
- QFracture tool: qfracture.org/
- NOGG guideline: www.sheffield.ac.uk/NOGG/
- ROS consensus: *Strong, steady, and straight.* Available at: theros.org.uk/clinical-publications-and-resources/

NOGG=National Osteoporosis Guideline Group;
ROS=Royal Osteoporosis Society

- Sequence of therapy should be planned with a bone specialist unit
- Primary care follow-up:
  - ensure treatment has been initiated and advice on lifestyle modifications has been given
    - advice on lifestyle modifcations should be repeated at each consultation
  - check adherence within 4 and at 12 months,[3,27] including:
    - tolerability
    - new cautions and contraindications
    - calcium/vitamin D intake
    - change in fracture and falls risk
  - continue to review medication and adherence annually and after 3 years assess the level of future risk through FRAX or QFracture (and measure BMD if required) according to local or national guidelines
    - more frequent reviews may be required if patient is prone to falling or re-fractures
    - practice-based pharmacists may undertake annual reviews as part of a medicines optimisation review and repeat prescribing; liaison with community pharmacists will enhance patient care.

Duration of therapy

- Sequence of therapy post bone-forming agents
  - after teriparatide and biosimilars of teriparatide treatment course of 24 months switch patients to antiresorptive therapy[18–20]
  - after romosozumab treatment course of 12 months switch patients to antiresorptive therapy[21]
- For denosumab the potential benefit-risk balance of treatment cessation is altered, and treatment switching should only be undertaken in consultation with a bone specialist; for other antiresorptive therapies, duration of therapy should be as per local or national guidelines with review of the risks versus benefits of discontinuing therapy[2,28,29]
  - SIGN recommends that in post-menopausal women, the following therapies can be continued for:[23]
    - 10 years—alendronic acid, strontium ranelate (if severe osteoporosis and other treatments are unsuitable), and denosumab
    - 7 years—risendronic acid
    - 3 years—zolendronic acid.

Acknowledgements

Jemma Lough, independent medical writer, helped draft this guideline.

Conflicts of interest

The group members have received an honorarium to develop this working party guideline. Some of the group members have also received consultancy fees from other pharmaceutical companies, which may include UCB Pharma Ltd, for activities other than the development of this working party guideline.

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Guidance during the COVID-19 pandemic

- In the absence of BMD measurements, do not delay initiating treatment for patients deemed high or very high risk; if appropriate, arrange a DXA scan when available
- Re-iterate the importance of calcium/vitamin D intake and home exercise while staying at home/self-isolating
- Falls prevention advice and exercise advice can be given remotely; provide the following link to patients for exercise videos on the ROS website: theros.org.uk/information-and-support/living-with-osteoporosis/exercise-and-physical-activity-for-osteoporosis/
- Follow up with care home patients with fragility fractures using telephone clinics
- Some patients will require face-to-face assessments, especially if they have learning difficulties or cognitive decline
- Re-iterate the importance of medication adherence to reduce fracture risk
- Denosumab treatment should be continued; if suitable, patients can be enrolled in the self-injection programme; refer to ROS guidance: theros.org.uk/healthcare-professionals/covid-19-hub/denosumab-prolia-treatment-and-the-covid-19-pandemic/
- COVID-19 guidance is also available from the IOF: www.capturethefracture.org/covid-19-all-ctf-fls-centers

BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; IOF=International Osteoporosis Foundation; ROS=Royal Osteoporosis Society