**Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group.**

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**Conflict of interest**

Lawrence Drudge-Coates has received honoraria from Amgen, AstraZeneca, Ipsen, Ferring, Astellas

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**Take home message**: Bone health assessment should be prioritised when men with prostate cancer start long-term ADT. Assessment of bone mineral density and fracture risk identifies those at risk, allows rapid initiation of treatment, and avoids skeletal complications with resulting morbidity and mortality.

**Abstract**

**Background and objective**

The incidence of prostate cancer (PC) is increasing alongside the ageing global population, and androgen deprivation therapy (ADT) and other therapies are increasing survival. Consideration of bone health is vital, to reduce the likelihood of fragility fractures and their associated morbidity and mortality. This guidance aims to summarise the evidence for assessment and management of bone health in this population, with specific recommendations for clinical practice.

**Methods**

A systematic literature review was followed by a meeting of key opinion leaders. Input and endorsement was also sought from patient and nursing representatives, and specialist societies.

**Summary of guidance**

ADT is associated with significant loss of bone mineral density (BMD). Chemotherapy and abiraterone are used alongside ADT in the metastatic setting, and require significant doses of concomitant corticosteroids. Both ADT and corticosteroids pose a significant challenge to skeletal health, in a population of patients who are likely to have ongoing bone loss related to age and/or comorbid conditions.

Current PC guidelines lack specific recommendations regarding supplementation with calcium and vitamin D, the role of fracture assessment and reassessment, intervention thresholds and selection of therapy.

All men starting long-term ADT (with our without metastatic bone disease) should receive lifestyle advice regarding their bone health. Calcium and vitamin D intake should be assessed with supplementation if required. All men should have their BMD measured and fracture risk calculated (FRAX) with the need for intervention checked against National Osteoporosis Guideline Group thresholds. Those below the intervention threshold should have BMD and FRAX repeated after 12-18 months. Those above the intervention threshold should be further assessed, with referral to a specialist centre if available, and offered appropriate pharmacological treatment.

**Introduction**

Bone health is emerging as one of the most important considerations for men receiving treatment for prostate cancer (PC). Projected to be the commonest cancer by 2030 1, 1 in 8 men will receive a diagnosis of PC in their lifetime. There are more than 400,000 new cases of PC in Europe each year, and the majority of these occur in men aged over 70 years 2. Despite the fact that PC is the second leading cause of cancer-related mortality in men 3, survival rates have improved considerably over the past four decades as a result of both earlier diagnosis and newer therapies (current 5- year survival is 85% in all patients, compared with 71% in 1980) 2.

Many patients with PC now live with their disease for many years, and consideration of the long-term consequences of treatment is increasingly important. Men with PC are not routinely referred to bone specialists for optimisation of their bone health, despite the fact that cancer treatment induced bone loss (CTIBL) and the resulting increased risk of fragility fractures (many of which require hospitalisation) is a significant issue 4. Although pathological fractures may occur in men with metastatic bone involvement, fragility fractures outweigh these by approximately 8:1 in all patients with PC 5,6. This guidance aims to provide non-bone specialists with evidence-based recommendations to support the assessment and management of bone health in men receiving PC treatment.

**1.1 Methodology**

*Expert group and specialist society involvement*

This guidance was developed by a group of experts, identified from key opinion leaders in the management of PC and bone disorders, including: medical and clinical oncologists, urologists, endocrinologists, rheumatologists, physicians specialising in metabolic bone disease, general practitioners, uro-oncology nurse specialists and patient representatives. Input and endorsement was also sought from a range of specialist societies during the process of guideline development: the National Osteoporosis Guideline Group (NOGG); National Osteoporosis Society; British Uro-oncology Group; Association of Cancer Physicians; European Association of Urology; European Society for Medical Oncology; Society for Endocrinology; and the British Association of Urological Nurses.

*Current guidelines*

National and international guidelines lack detailed, specific recommendations for the management of bone health in men receiving treatment for PC. The UK National Institute for Health and Care Excellence (NICE) Clinical Guideline for the management of PC makes general recommendations; that fracture risk is considered for all men receiving ADT and that treatment is offered to all those with osteoporosis 7. An updated version is due to be published in 2019, and recommends use of zoledronic acid in men with hormone refractory disease to prevent or reduce the risk of skeletal related events and/or to provide pain relief 8. However there is no mention of bone health assessment at the time of ADT initiation.

Joint European Association of Urology, European Society for Radiotherapy and Oncology and International Society for Geriatric Oncology PC guidelines suggest that BMD assessment is undertaken prior to the initiation of long-term ADT, and that the FRAX® tool should be used to estimate individual fracture risk 9 . There is no current guidance as to the intervention thresholds that should be used to initiate treatment, or the most appropriate pharmacological therapy. It is often unclear as to who should have overall responsibility for managing bone health in this group of patients, many of whom will be managed in a multi-disciplinary setting across both primary and secondary care.

*Definition of scope*

An initial meeting of expert group members was held, where the scope of the guidance was defined.

* To address the need for specific guidance for the management of PC treatment induced bone loss (including intervention thresholds) in a European setting
* To summarise the evidence supporting the management of bone health during PC treatment for non-bone specialists (including general practitioners, urologists, oncologists and specialist nurses) involved in the care of patients with PC at risk of cancer treatment-induced bone loss
* Using the UK as an exemplar, to sit the PC guidance alongside the NICE- accredited National Osteoporosis Guidance Group Clinical Guideline (2017) for the prevention and treatment of osteoporosis and the NICE guidance for the diagnosis and management of prostate cancer (NICE Clinical Guideline 175)

The group recommended that guidance should be available as an electronic download, along with a summary algorithm.

*Search strategy*

An initial systematic literature search was undertaken in 2012 using PubMed and Ovid MEDLINE databases using search terms chosen by the expert group (Appendix 1). The search was limited to articles published in English between January 2000 and March 2012. Randomised controlled trials, observational studies and meta-analyses were included for assessment. The search was repeated in July 2018, and key publications were added by members of the expert group for inclusion.

*Selection of evidence*

Following the initial literature search, abstracts were screened for relevance. Assessment of potentially relevant articles was conducted by at least two members of the expert reference group, with any disagreement resolved by consensus after discussion.

**1.2 Prostate cancer and bone loss**

*Prostate cancer treatments associated with bone loss*

*Androgen deprivation therapy*

Androgen deprivation therapy (ADT) is offered to men with PC in several different clinical settings, including; men who present with or progress to metastatic disease (continuous ADT); men who receive radical radiotherapy for localised or locally advanced disease (temporary ADT); and men who progress during a period of watchful waiting who are not fit for radical treatment (palliative continuous ADT). These indications are based upon clear evidence from large randomised clinical trials 10,11,12,13.

ADT is most commonly achieved by the administration of luteinising hormone releasing hormone (LHRH) agonists (such as goserelin and leuprorelin) and LHRH antagonists (such as degarelix). Antiandrogens (such as bicalutamide) may also be used.

Following initiation of ADT, sex steroid levels decrease rapidly and substantially (with the exception of bicalutamide). This reduction in circulating androgens and oestrogens disrupts the bone remodelling balance, stimulates osteoclast activity, decreases osteoclast apoptosis, and increases apoptosis of osteoblasts, all of which lead to net bone loss. Oestrogen decreases bone resorption, and its importance in skeletal homeostasis was highlighted by studies of male patients unable to produce or respond to serum oestrogen, who had both significantly increased bone turnover and incidence of osteopenia. A large randomised controlled trial is currently in progress to determine the safety and efficacy of transcutaneous oestrogen as an alternative to ADT (LHRH agonists) in men with PC: <http://www.isrctn.com/ISRCTN70406718>.

Evidence suggests that even before ADT is initiated, men with PC may have lower baseline bone mineral density (BMD) than age-matched controls 14 . Prospective studies have found that loss of BMD is most rapid during the first year of ADT (5-10% BMD loss) 15,16,17,18, and is greater than both normal age-related bone loss (0.5-1.0% per annum) and bone loss in postmenopausal women.

Bone loss continues, although at a less rapid rate, throughout the duration of ADT. Ongoing CTIBL in men with PC is superimposed upon normal age-related bone loss (more than half of men diagnosed with PC are aged over 70 years). It is more likely that older men will also have risk factors for fragility fracture other than ADT, such as risk of falls and comorbid conditions.

In addition to ADT-mediated effects on BMD, evidence suggests that ADT is associated with significant disruption to bone microarchitecture (for example, changes in cortical area and cortical porosity) 19. As microarchitecture is an important determinant of whole bone strength (independent of BMD), this further compromises bone strength in men receiving long-term ADT.

In addition to its direct effects on bone, ADT also affects body composition. Adiposity is substantially increased along with a decrease in lean body mass within 3-12 months of ADT initiation 20. Sarcopenia, defined as a progressive impairment of muscle function due to loss of skeletal muscle mass, increases the risk of falls, fractures and consequent loss of function or independence 21.

*Chemotherapy*

In the setting of metastatic hormone-sensitive PC, recent evidence has demonstrated a survival benefit when upfront chemotherapy is given alongside ADT 22 . Therefore, all men in this situation who are fit enough are currently offered six cycles of docetaxel. Corticosteroids are given alongside each cycle of docetaxel to reduce the risk of allergic reaction and to mitigate against some of the adverse effects. These are given as pre-medication (local protocols vary but usually between 30-40mg dexamethasone) and as a daily dose of prednisolone (10mg per day) for 21 days 22.

*Other systemic therapies*

Abiraterone acetate is a selective androgen synthesis inhibitor. Inhibition of cytochrome P450 17 alpha-hydroxylase (CYP17A1) blocks androgen production in the testes, adrenals and prostate tumour tissue. As this also blocks the production of glucocorticoids, prednisolone (usual dose 10mg/day) is given together with abiraterone. It is recommended for use in men with metastatic castration resistant prostate cancer (mCRPC)23. Abiraterone has also been found to improve survival in men with newly diagnosed hormone sensitive metastatic prostate cancer (compared to ADT alone) 24,25. It is currently approved by the United States Food and Drug Administration and the European Medicines Agency, and recommended by both ESMO and EAU for use in this setting 26–28.

Enzalutamide is an oral androgen receptor inhibitor that is currently used in men with mCRPC 29. Unlike abiraterone it does not require concomitant corticosteroids. Recent data suggest that it may have a future role in the management of non-metastatic castration resistant disease 30.

* 1. **Glucocorticoids and bone loss**

The long-term use of glucocorticoids is one of the commonest causes of secondary osteoporosis. In addition to their use with chemotherapy and abiraterone, they may also be used in a palliative setting when all standard treatment options for PC have been used. The underlying pathophysiology involves increased osteoblast and osteocyte apoptosis, and decreased osteoblastogenesis. There is also a transient increase in osteoclast survival and osteoclastogenesis when glucocorticoids are initiated. As a consequence of increased bone resorption, decreased formation and interruption of regulatory pathways, there is an early and rapid loss of BMD and bone quality, and a significantly increased risk of fracture 31. The risk of hip and vertebral fractures increases up to 7- and 17- fold respectively when doses equivalent to 10-12mg prednisolone are given for more than 3 months 31. The risk of fracture is also increased even when small (2.5-3mg) daily doses are given 31. No studies to date have investigated the impact of the combination of docetaxel and glucocorticoids, or other systemic therapies on bone health or risk of fracture in men with PC.

**1.4 Osteoporosis**

*Background*

Osteoporosis is defined as a progressive systemic skeletal disorder, characterised by low bone mass andmicroarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture 32. The prevalence of osteoporosis increases with age, due to both age-related loss of bone mineral density (BMD) (0.5%-1.0% BMD per year) and the presence of additional factors that accelerate bone loss, such as the menopause, lifestyle factors, presence of comorbid conditions and use of medications that have direct effects on bone.

In Europe, there are 22 million women and 5.5 million men living with osteoporosis, which is responsible for 3.5 million fragility fractures per year. The economic burden of both incident and prior fragility fractures has been estimated at €37 billion, with the majority of the costs being accrued in the first year 33.

Fragility fractures arise as a consequence of low energy mechanical forces that would not ordinarily cause fracture (equivalent to a fall from standing height or less), and most commonly affect the proximal femur (hip), vertebrae and distal radius 34. More than one in three of adult women and one in five men will sustain one or more fragility fractures in their lifetime 35. Such fractures are also a major predictor of subsequent fracture, the risk of which increases at least two-fold after a previous fracture, and is partially independent of BMD.

Hip fractures are the most serious fragility fracture, and pose a considerable challenge to health and social care provision. They usually occur after a fall from standing, but may also occur spontaneously. There are more than 600,000 new hip fractures in Europe each year 36, a figure which is projected to increase significantly by 2050 as a result of the ageing population 37. In the United Kingdom, hip fractures account for almost 70,000 unplanned hospital admissions and 20% of orthopaedic bed occupancy 38. They are an important cause of morbidity, often resulting in significant pain, disability and loss of independence. More than 50% of patients will be unable to live independently following discharge from hospital, and only 30% will fully recover. The association between hip fracture and mortality is well established, with around one third of patients dying within 12 months 39. Mortality following hip fracture is significantly higher in men 40,41.

Other common and important sites of fragility fracture are the vertebrae and upper limb 42. Vertebral fractures are frequently under-diagnosed, and often detected incidentally or as a result of investigations following another type of fracture. Vertebral fractures cause pain, limited activity, height loss and respiratory compromise, and are associated with increased mortality. Upper limb fractures are less likely to result in hospitalisation, but are often associated with considerable impact on ability to self care (degree of impact depends on whether the dominant side is fractured), increased carer burden, lasting impact on acivities of daily living, and chronic pain.

*Definition and diagnosis*

The World Health Organization (WHO) definition of osteoporosis, launched in 1994, is based upon bone mineral density (BMD). Fracture risk increases progressively with decreasing BMD, with approximately a twofold increase in risk with each standard deviation (SD) decrease in BMD 43, 44. Using dual energy X-ray absorptiometry (DXA), a T-score of 2.5 SD or more below the mean value for young healthy adults is diagnostic of osteoporosis 32. The proximal femur (total hip or femoral neck) is an important site to assess, due to its higher predictive risk for fracture, and relatively low prevalence of degenerative change (which artificially increases BMD measurements at the spine) 45. BMD should also be measured in the lumbar spine (L1-L4) in all patients46. However, its accuracy may be impaired in older patients by the presence of degenerative disc disease, osteophytes and aortic calcification, all of which may artefactually increase BMD. DXA has the advantage that it is widely available and uses low dose radiation, however, it cannot be used in isolation to predict those at high risk of fracture, due to important limitations.

BMD testing is highly specific but has low sensitivity for fracture prediction; many individuals who sustain a fracture are subsequently found to have non-osteoporotic BMD. Most fragility fractures will therefore occur in those who do not have osteoporosis as defined by a T-score ≤-2.5 47. Several other factors that are BMD-independent may also contribute to the risk of fracture. These include; age, sex, increased risk of falls, previous fracture, family history of fracture, and other lifestyle factors. Fracture risk assessment tools such as FRAX® and QFracture have been developed, which integrate these variables with other information in order to determine risk of fracture.

**1.5 Management of CTIBL in prostate cancer**

*Patient and clinician education*

Current evidence suggests that men with PC receiving ADT often lack basic osteoporosis knowledge and do not actively seek to take measures to optimise their bone health 48 49. Provision of individualised, patient-centred information can improve knowledge and engagement with appropriate lifestyle modifications 48. Published surveys of urologists and clinical oncologists have found that clinicians lack confidence in providing self-management advice to patients to optimise bone health, and do not feel able to effectively manage men who are identified as having abnormal BMD 50,51 .

*Lifestyle factors*

Both smoking and excessive alcohol intake reduce the BMD of men with PC, and should be avoided 52. It has been demonstrated that exercise improves muscular strength, cardiorespiratory fitness, lean body mass, fatigue, and quality of life in men receiving treatment for PC 53, 20. The UK National Institute for Health and Care Excellence (NICE) Clinical Guideline 175 for PC recommends that all men starting or having ADT should be offered supervised resistance and aerobic exercise at least twice a week for 12 weeks 7.

*The role of calcium and vitamin D*

Daily calcium intake (DCI) is inadequate in the majority of older men with PC 54. The NOGG recommends a DCI between 700 and 1200mg, achieved where possible through dietary intake but supplements may also be used should this not be possible. DCI may be calculated using an online tool such <http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator>.

Vitamin D deficiency (serum 25-hydroxyvitamin D (25-OHD) level <25 nmol/L)) affects more than a quarter of older men, with up to three quarters found to have insufficiency (25-50 nmol/L) 55. In combination with calcium, vitamin D supplements are associated with a small reduction in hip and non-vertebral fractures in older men 56,57, and may also reduce the risk of falls 58. NOGG recommends vitamin D supplementation with 800IU daily in all men aged over 50 at increased risk of fracture 59.

No studies have specifically examined the effect of calcium and/or vitamin D supplementation upon loss of BMD associated with ADT. However, studies of various bone targeted agents in men with PC have used calcium and vitamin D supplementation in both treatment and control arms 60 61 . Currently recommended doses of calcium and vitamin D were found to be insufficient to prevent bone loss associated with ADT 62. No subsequent trials have sought to determine the safety or efficacy of using higher doses in this population.

*Bone targeted agents*

*Bisphosphonates*

Several randomised studies have investigated the ability of bisphosphonates to reduce BMD loss associated with ADT. (Table 1) 63–74. Bisphosphonates including pamidronate sodium, neridronic acid, risedronate sodium, zoledronic acid and alendronate have been shown to be effective in the prevention of BMD loss at the lumbar spine (LS), femoral neck and total hip. The largest and most recent study included 186 men with locally advanced PC randomised to receive alendronate or placebo 71. The mean change in LS BMD was +1.7% in the alendronate group and -1.9% with placebo (p<0.0001), with a significant reduction in biomarkers of bone turnover (BTM) in those receiving bisphosphonates, and a similar rate of adverse events.

However, published studies to date have had important limitations including; small patient numbers, heterogeneous populations, variation in type and frequency of bisphosphonate administration, and varying follow-up schedules. No study has been sufficiently powered to detect differences in fracture incidence alone. Only one non-randomised study has sought to compare efficacy of different bisphosphonates 75.

A meta-analysis of 15 randomised studies including 2,634 patients receiving ADT for PC sought to determine the fracture rate, changes in BMD, incidence of osteoporosis, and adverse events associated with bisphosphonate use 76. Treatment with bisphosphonate had a substantial effect in both fracture prevention (RR 0.8, 95% CI 0.69 to 0.94, *p*=0.005) and osteoporosis reduction (RR 0.39, 95% CI 0.28 to 0.55 for total analysis, *p*<0.00001). Most studies that compared zoledronic acid with placebo used a 4mg dose administered 3 monthly. However, the usual recommended dose is 5mg annually for the treatment of osteoporosis that is not related to ADT, and the optimal dosing schedule is unclear. There were no significant increases in major adverse events associated with bisphosphonate treatment, which the authors concluded was safe and effective in the prevention of CTIBL in men with PC receiving ADT.

Although evidence suggests that bisphosphonates may have a role in the preservation of BMD in men receiving ADT for PC, no bisphosphonate is currently approved for this purpose. Large, prospective randomised studies are required to determine which bisphosphonate has greatest efficacy and cost-efficacy in the prevention of CTIBL, optimal dosing schedules, and detection of differences in fracture risk reduction.

*Denosumab*

A placebo-controlled trial of denosumab in 1,468 men receiving ADT for non-metastatic PC found that 60mg denosumab administered subcutaneously every 6 months increased LS BMD by 5.6% after 24 months, whereas treatment with placebo was associated with a 1.0% reduction (p<0.001) 77. Denosumab was also associated with a reduced incidence of new vertebral fractures after 36 months (1.5% with denosumab versus 3.9% with placebo; RR 0.38; 95% CI 0.19–0.78) and a non-significant decrease in fracture incidence at any site. Further subgroup analysis reported that denosumab was associated with significant and consistent increases in BMD at all sites, and in every subgroup analysed (including older men, longer ADT duration, lower baseline T scores, biomarkers of bone turnover, and prevalent vertebral fractures) 77. Patients that received denosumab also experienced a significant suppression of BTM compared with placebo 78.

A randomised study in 234 men with PC receiving ADT and a T score <-1.0 compared denosumab with weekly alendronic acid for 2 years 79. Denosumab was superior in terms of improved LS BMD after 2 years (+5.6% in denosumab group vs -1.1% with alendronic acid, *p*<0.001). Incidence of vertebral fractures, pain reduction and adverse events were similar. On the basis of these results, denosumab has been authorised by the European Medicines Authority for use in the prevention of CTIBL associated with ADT.

Bisphosphonates and denosumab are associated with similar adverse effects, the most serious of which is osteonecrosis of the jaw (ONJ). Studies of denosumab in men with both metastatic PC and non-metastatic CRPC have reported an ONJ incidence of 5% or less 80,81. Similarly, the frequency of ONJ with bisphosphonate use in men with PC is 1-2% 81,82. These are based on doses used in metastatic bone disease (4mg zoledronic acid or 120mg denosumab every 4 weeks). The incidence of ONJ in the osteoporosis patient population is significantly less, estimated at between 0.001% and 0.01% 83. Both denosumab and bisphosphonates are also associated with an increased risk of hypocalcaemia. When denosumab is given twice yearly to men with PC on ADT, the incidence of hypocalcaemia is reported as less than 1% 60.

Other pharmacological treatments for osteoporosis (including the selective oestrogen receptor modulators raloxifene and toremifene) are not currently recommended to prevent bone loss in men with PC receiving ADT. Teriparatide (recombinant PTH) is contraindicated in patients with metastatic bone disease and in those who have received prior radiotherapy.

**Table 1: Randomised studies of the effect of bisphosphonates in men receiving ADT for PC**

Abbreviations: PC: prostate cancer; BM: bone metastasis; MAB: maximum androgen blockade; ADT: androgen deprivation; LS: lumbar spine; BMD: bone mineral density; OP: osteoporosis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **Study population** | **N** | **Study groups** | **Follow-up** | **Key findings** |
| 200163 | Locally advanced or recurrent PC | 47 | Pamidronate + ADT vs ADT only | 48 weeks | No significant BMD change in pamidronate group  Significant loss of BMD at LS and hip in ADT only group (-3.3% and -1.8%, p<0.001) |
| 200164 | Metastatic PC | 21 | MAB + pamidronate vs MAB | 12 months | Significant increase in LS (+7.8% vs -5.7% p=0.0001) and femoral neck (+2.0% vs -2.3% p=0.0007) BMD in pamidronate group compared to MAB group |
| 200367 | Non-metastatic PC | 106 | Zoledronic acid + ADT vs ADT | 12 months | Zoledronic acid associated with increased LS BMD compared to ADT alone (5.6% Vs -2.2%, p<0.001) |
| 200568 | Locally advanced PC, OP at baseline | 60 | MAB vs  MAB + neridronic acid vs bicalutamide vs bicalutamide + neridronic acid | 12 months | MAB group experienced significant BMD loss at LS and hip (-4.9% and -1.9%; p=0.002 and 0.004 respectively)  No BMD change in the MAB and neridronic acid group  Non-significant BMD loss in bicalutamide group  BMD increase at LS (+2.5%; p<0.05) and hip (+1.6%; p<0.05) in bicalutamide + neridronic acid group |
| 2006 69 | Non metastatic PC and received ADT < 12 months | 120 | Zoledronic acid + ADT vs placebo + ADT | 12 months | Increase in LS and hip BMD in zoledronic acid group compared with placebo (p<0.0001 for both) |
| 200770 | Localised and metastatic PC receiving ADT <12 months | 42 | Zoledronic acid + ADT vs placebo + ADT | 12 months | Increase in LS (+4.9% vs -2.2% p<0.0001) and femoral neck (0.9% vs -3.2% p<0.0001) BMD in zoledronic acid group compared with placebo |
| 2007 /8 73,74 | Non-metastatic PC | 112 | Alendronic acid + ADT vs  placebo + ADT  (crossover at 12 months) | 24 months | BMD increased at LS and hip with alendronic acid, and decreased with placebo (p<0.001) at 1 year  At crossover, significant LS and hip BMD gains continued during second year of alendronic acid.  BMD maintained at hip and spine in those who switched to placebo, but BMD loss at radius. |
| 200765 | Non-metastatic PC receiving ADT | 44 | Zoledronic acid + ADT vs placebo + ADT | 12 months | Increase in hip (+4.0% vs -3.1% p<0.001) and LS (+0.7% vs -1.9% p=0.004) BMD with zoledronic acid compared with placebo |
| 200966 | Non metastatic PC initiating or already receiving ADT | 93 | Zoledronic acid + ADT vs placebo + ADT | 12 months | Increased LS BMD with zoledronic acid in those receiving ADT for <1year (+5.12% vs -3.13% with placebo, p=0.0029) and in those receiving ADT for more than 2 years (+4.82% vs +0.99% with placebo, p=0.0013) |
| 2013 72 | ADT for 2-3 years and OP | 104 | Risedronate + ADT vs  placebo + ADT | 2 years | Decreased LS BMD in both groups, no significant difference between groups |
| 2013 71 | Localised PC | 186 | Alendronic acid + ADT vs placebo + ADT | 12 months | Significant increase in LS BMD with alendronic acid (+1.7% and -1.9% with placebo, p<0.0001) |

**1.6 Fracture risk assessment tools**

Risk assessment tools are available to determine the risk of fragility fracture on an individual basis. Additional clinical risk factors contribute to the risk of fracture at least partially independently of BMD (most fractures occur in individuals subsequently found to have non-osteoporotic BMD). The two most frequently used tools are the Fracture Risk Assessment Tool (FRAX® available at https://www.sheffield.ac.uk/FRAX) and QFracture (https://qfracture.org); however, neither has been specifically developed for use in men with PC. QFracture does not incorporate BMD assessment, whereas FRAX® may be used with or without it. NICE have recommended FRAX® should primarily be used where DXA is available, in order to provide a BMD value to integrate into the risk calculation (described later).

Fracture risk assessment tools estimate the 1 to10-year probability of both hip fracture and major osteoporotic fracture (hip, spine, wrist or humerus). Short-term risk is preferable to calculating lifetime risk due to several factors; assumptions regarding future mortality become increasingly uncertain after 10 years; interventions are not usually given for life but for a period of a few years; and the long-term prognostic value of risk factors may decrease over time.

*QFracture*

QFracture is based on a prospective open cohort study of routinely collected data from general practice and considers several fracture risk factors. The tool is available online, and can be used to estimate the 1-10-year cumulative incidence of hip or other major osteoporotic fractures. There are no published intervention thresholds using the QFracture tool.

*FRAX*®

*FRAX*®, developed by the then WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield was launched in 2008 and is based upon primary data from 12 prospectively studied population based international cohorts. Follow-up was extensive, and included more than 60,000 patients and 5,000 fractures, with subsequent external validation in a further 11 cohorts comprising 230,486 individuals. Given the historical focus of osteoporosis on women rather than men, it is unsurprising that men comprise only a minority of the original *FRAX*® cohorts (25%). There has been much debate as to whether the gradient of risk (change in risk of fracture per SD change in BMD) or the absolute risk (risk of fracture at a given T-score) differs between men and women. Current evidence suggests that the risk appears to be the same in both sexes, and the tool has been shown to be of predictive value in both male and mixed gender cohorts 84.

*FRAX*® is currently the most widely used fracture risk assessment tool in clinical practice, and has been incorporated into an increasing number of guidelines worldwide 85,86,87,88. A range of clinical risk factors along with age and sex are included in the algorithm, which can be accessed online (Figure 1) 89. Anticancer treatments are not currently included as a specific risk factor.

As fracture probability differs markedly in different regions of the world, FRAX® models are available to calibrate the tool for use in various countries where the epidemiology of fracture and death are known. Unlike other algorithms, FRAX® computes fracture probability taking both the risk of fracture and risk of death into account. This is important because some of the risk factors affect the risk of death as well as the fracture risk. Examples include increasing age, low body mass index (BMI), low BMD, glucocorticoids and smoking. In addition to providing an estimate of risk, the FRAX® website in some country models has a link to national guidance for the management of osteoporosis, such as the UK National Osteoporosis Guideline Group (NOGG) in the UK.

FRAX has recently been shown to be predictive of falls in elderly men 90. This is of particular significance in older men receiving ADT for prostate cancer, as ADT alters body composition. As well as increasing the risk of falls, sarcopenia also decreases rehabilitation potential in the post-fall setting 91.

*FRAX*® *and ADT*

ADT is not included as a specific risk variable within FRAX. There is insufficient evidence that ADT is independently associated with fracture risk as calculated using FRAX® (particularly when BMD is included). Multivariate analysis of the placebo arm of a prospective study of toremifene, (with ADT duration included as one of the variables) reported that older age and lower BMD were the only statistically significant independent predictors of fracture risk 92. A population-based prospective study in men (including 43 men with PC), found that older age, lower BMD and increased rate of bone loss were the only significant predictors of fracture risk 93. An on-going collaboration between some authors of this guidance aims to determine the fracture risk in a large (over 7,000 men) cohort of patients who are currently participating in the STAMPEDE trial 94. It is hoped that this analysis will identify the extent of the risk in this population and better inform future guideline development and service delivery plans.

A conservative assumption would be that the modification of fracture risk by ADT is captured almost completely by its impact on BMD. The secondary osteoporosis variable in FRAX® already serves this function. This variable contains a number of risk factors that have been shown to be associated with fracture risk (RR 1.3-1.7) but with little or no evidence that this risk is truly independent of BMD. Thus, once BMD is entered to the calculation, no further weight is accorded to the presence of this risk factor. Secondary causes are distinct from rheumatoid arthritis, where there is good evidence the disease itself conveys an increase in fracture risk that is not completely captured by BMD, BMI or glucocorticoid use. As for any clinical prediction tool, interpretation should be tempered by additional information of clinical significance; such as a high falls risk, multiple prior fractures, immobility and severe rheumatoid arthritis 95.

*Intervention thresholds*

Approaches used to set intervention thresholds depend on local factors such as reimbursement policies, health economic assessment, willingness to pay for health care in osteoporosis and access to DXA 96–98. Most recommendations for intervention thresholds in osteoporosis are based on postmenopausal osteoporosis where there is an established evidence base. In the UK, NOGG has included the management of male osteoporosis in their most recent guidance 59.

NOGG takes the approach that most guidelines recommend that postmenopausal women with a prior fragility fracture may be considered for intervention without the absolute need for a BMD test (a BMD test may be independently requested to monitor treatment)99–101. In the UK, the age-specific FRAX® intervention threshold is set to that of women with a prior fracture; the corollary is that women without fracture but with a similar or greater age-specific fracture probability would merit consideration for treatment. The threshold rises with age until the age of 70 years, and at 70 years and above fixed thresholds are applied (Figure 2) 102. In light of the fact that it would be difficult to justify a different (i.e. lower) intervention threshold in men, it is logical to apply the same thresholds in both men and women. Some countries have decided to apply a fixed, age-independent threshold for intervention, largely driven by a health economics analysis from within the US which might not be appropriate within other healthcare settings 99.

*Assessment of fracture risk*

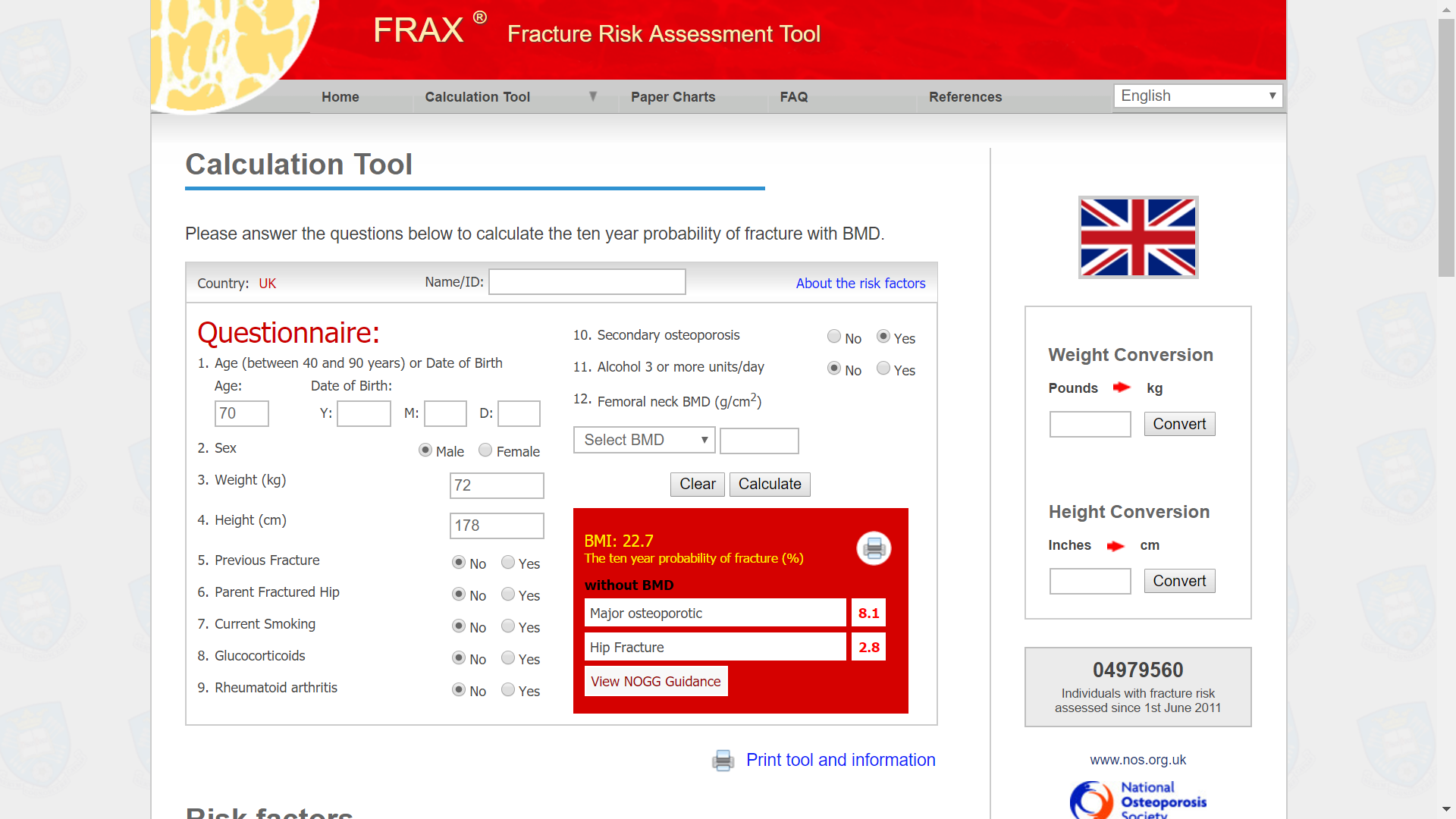
To minimise the risk of fracture in men receiving treatment for PC, all men (irrespective of whether they have metastatic bone disease) should have their BMD measured at the time of ADT initiation. Men with a previous fracture and/or who are found to be osteoporotic should have further investigations to exclude causes of secondary osteoporosis as treatment of underlying causes (for example malabsorption or liver disease) form part of the overall management. This may best be achieved by referral to appropriate services (metabolic bone/ endocrinology). The femoral neck BMD result is used in FRAX to calculate the 10 year probability of major osteoporotic fracture 34,97,102. Using the NOGG threshold (Figure 2), men with probabilities above the upper threshold should be offered treatment.

*Dosing regimens*

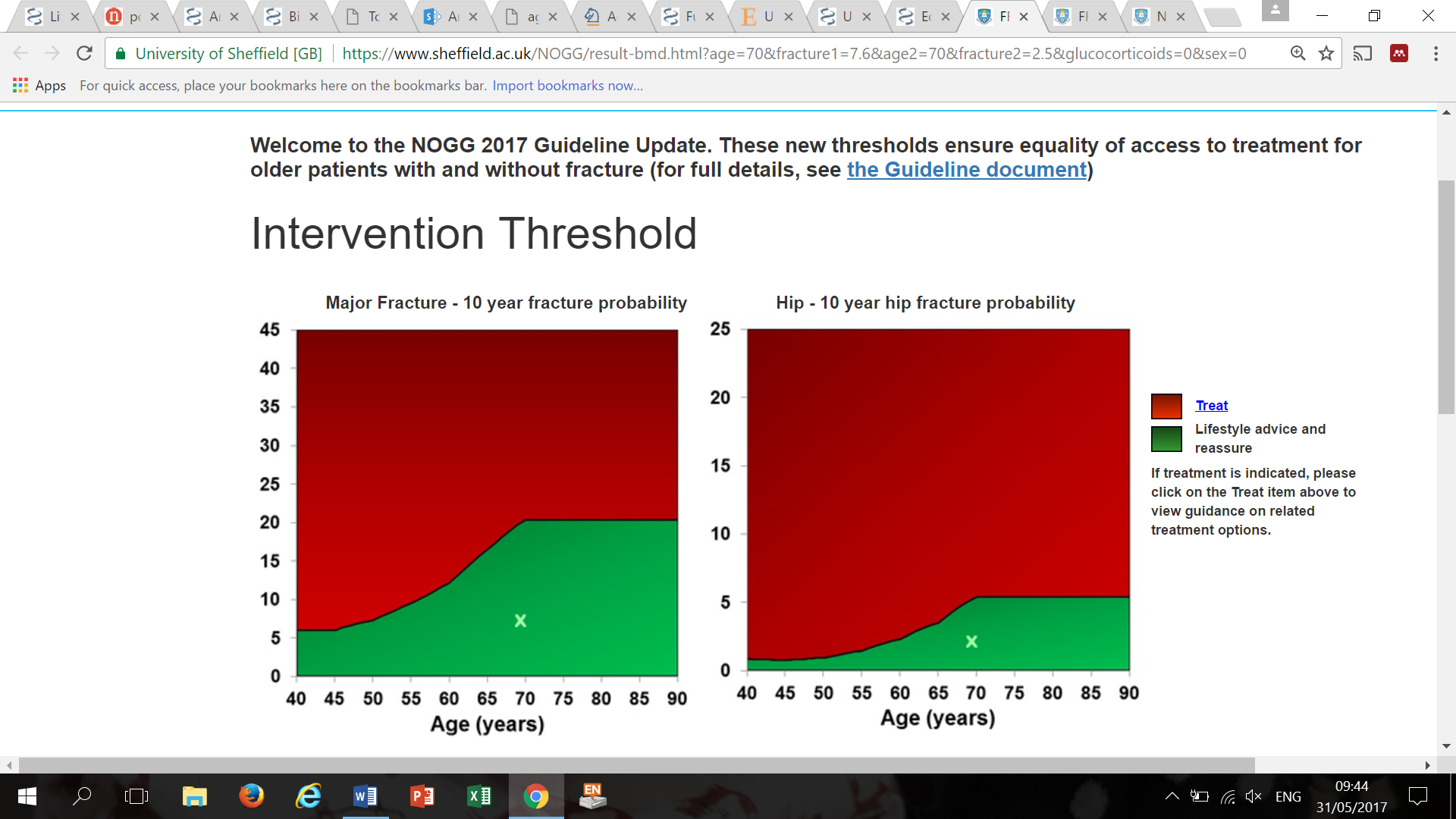
NOGG recommends oral bisphosphonates such as alendronic acid (10mg daily) or risedronate sodium (5mg daily) for osteoporosis in men. If compliance with daily therapy is poor, weekly oral bisphosphonate therapy is an alternative. When oral therapy is not feasible or tolerated, intravenous zoledronic acid may be used (5mg once yearly), or denosumab may be given subcutaneously at a dose of 60 mg once every 6 months.

*Reassessment of fracture risk*

In men found to lie below (but close to) the intervention threshold, a reassessment including a repeat BMD should be undertaken after 12-18 months of ADT.

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**Figure 1:** Screenshot of the UK FRAX® tool showing a calculation of major fracture and hip fracture probability in a man aged 70 years with secondary osteoporosis (e.g. prostate cancer on ADT) 89.

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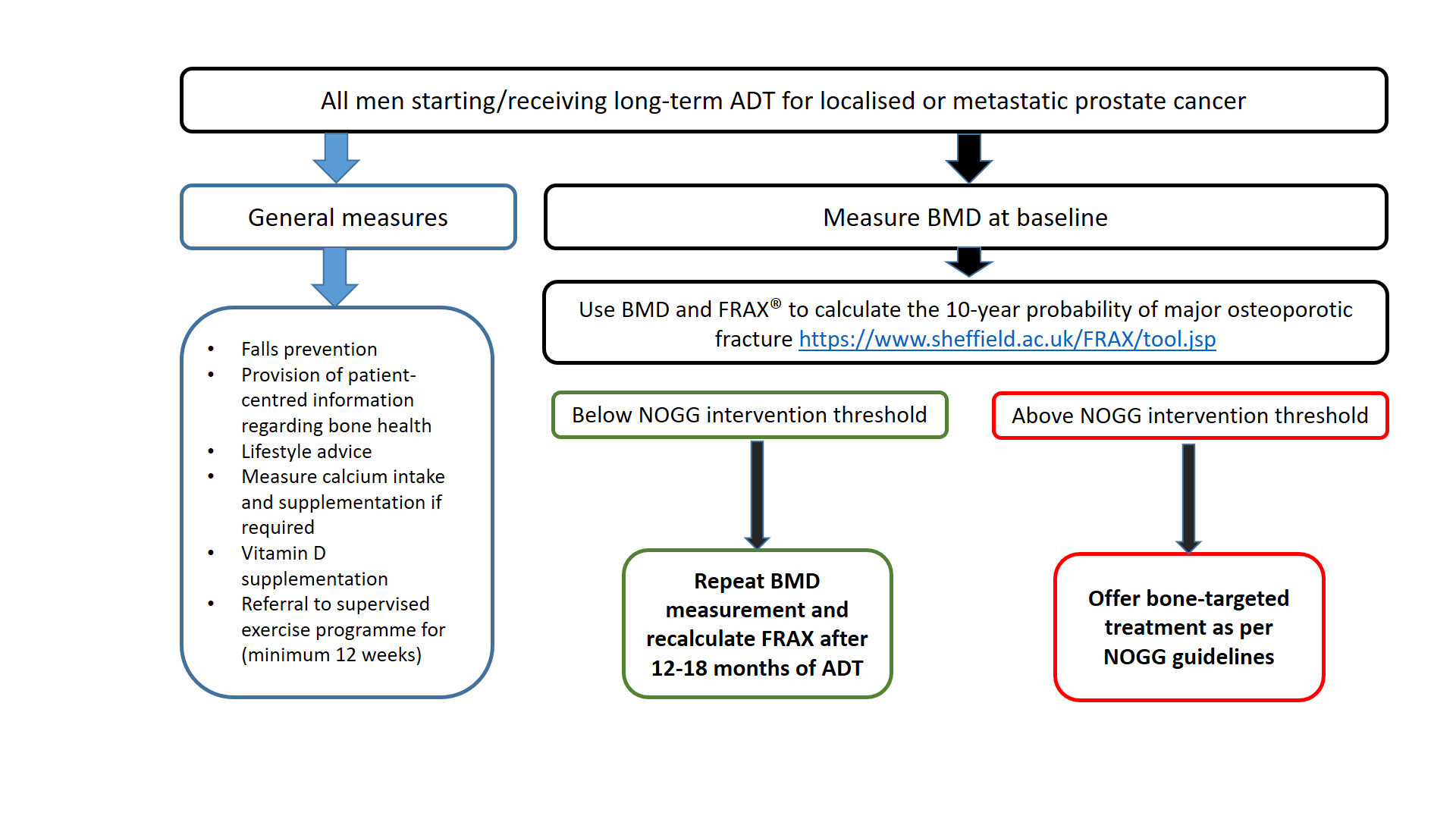
**Figure 2: NOGG intervention thresholds.** The thresholds depicted by the lines between the green and red areas above are the 10-year probabilities of a major osteoporotic fracture (left graph) or hip fracture (right graph) in women with a previous fracture. Treatment should strongly be considered in those with fracture probabilities at or above the threshold.

**1.7 Recommendations**

All men starting long-term ADT for PC (with or without metastatic bone involvement) should:

* Be provided with individualised and patient-centred information, including appropriate lifestyle advice regarding optimisation of bone health
* Be referred to a supervised resistance and aerobic exercise programme of at least 12 weeks duration (in accordance with NICE guidelines)
* Have daily calcium intake calculated to identify need for supplementation (using a tool such as the Edinburgh calculator) <http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator>
* Achieve or maintain adequate daily calcium (700- 1200mg) and vitamin D (800 IU) intake through dietary intake, sunlight exposure, and supplementation
* Undergo DXA to assess BMD when ADT is commenced
* Have their fracture risk assessed using FRAX® with BMD to determine 10-year probability of major osteoporotic and hip fracture <https://www.sheffield.ac.uk/FRAX/tool.jsp>;
* Those found to have a high probability of fracture as defined by NOGG treatment threshold should be offered appropriate pharmacological treatment. Choice of therapy should follow current NOGG guidance https://www.sheffield.ac.uk/NOGG/index.html: oral alendronate and risedronate, denosumab (subcutaneous) or zoledronic acid (intravenous)
* Those below the intervention threshold should have their BMD reassessed after 12-18 months of ADT
* Be investigated for other causes of secondary osteoporosis if BMD is within the osteoporosis range; this can best be achieved by referral to specialist centres for on-going management

**Algorithm**



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