OSTEOPOROSIS - Medical Management of Adults

Use FRAX® assessment tool to assess fracture risk
(see page 4 of guidelines)

http://www.shef.ac.uk/FRAX
then
use the link to NOGG guidance

Measure BMD if recommended and recalculate fracture risk

FRAX result below treatment threshold line;	FRAX result above treatment threshold line;
Consider risks & benefits for treatment with bisphosphonates (NICE TA464)	Investigate[A] and **Advise treatment**
Reassure, General measures[B],	
Reassess fractured risk in ≤ 5 yrs	

[A]Investigations
- FBC, ESR (If ESR raised, measure serum paraproteins and urine Bence Jones protein)
- Bone and liver function tests (Ca, P, Alk phos, albumin, ALT)
- Renal function
- Serum 25 0H Vit D
  Consider PTH if:
  - Calcium level raised
  - Calcium level in upper quartile of normal range and vitamin D deficient

  Additional tests if indicated:
- Serum TSH
- Coeliac screen (TTG)
- Serum testosterone, LH and SHBG, PSA (men)
- Consider γGT
- Lateral thoracic and lumbar spine X rays
- BMD if monitoring required
- Consider Isotope bone scan

[B]General measures
- Recommend good nutrition esp. with adequate calcium and vitamin D (see link to dietary calcium calculator)[15]
- Recommend regular weight bearing exercise
- Maintain ideal body weight
- Avoid tobacco use and alcohol abuse
  Assess falls risk and give advice if appropriate

If frail, increased falls risk ± housebound bone agents in the flow diagram may not be indicated

Advise calcium 1 – 1.2 gram and colecalciferol 20 micrograms (800 units) daily (e.g. Adcal D3 chewable tablets 1 tablet twice daily)

Assess falls risk.
Advise or refer to Falls Service as

Advise Treatment
ALENDRONATE tablets
70mg WEEKLY (*1st Line*)

Advise three/six monthly review of adherence to therapy as non-compliance is common.
Seek specialist opinion if patient sustains a fracture after 1 year on compliant therapy.

RISEDRONATE tablets 35mg WEEKLY recommended for glucocorticoid-induced osteoporosis (GIO)

Consider any of the following 2nd line treatments if alendronate not suitable because patient
- unable to comply with the special instructions for the administration of alendronate
- has a contraindication to, is intolerant of, or has a lack of clinical response to alendronate

ALTERNATIVE BISPHOSPHONATE	DENOSUMAB	RALOXIFENE
Refer to Page 4 of guidelines	60mg s.c. injection Administered every 6 months Refer to page 6 of guidelines	60mg daily Refer to page 7 of guidelines

Specialist Initiated Teriparatide (refer to page 7 of guidelines)

All patients should be prescribed
Calcium 1 – 1.2 gram + colecalciferol 20 micrograms (800 units) daily
unless clinician is confident dietary calcium intake is adequate (approx. 1gram per day) and patient is vitamin D replete. (see link to dietary calcium calculator)[15]. Prescribe colecalciferol 800 units daily alone in patients with adequate calcium intake who only need vitamin D supplement.

Clinical Risk Factors For Osteoporosis

- Previous fragility fracture
- Current glucocorticoid use ≥ 3 months and frequent past
- Parental history of hip fracture
- Radiographic osteopenia
- Height Loss > 3.0 – 5.0 cm
- Female hypogonadism
  - post-menopause
  - untreated premature menopause
  - drug or surgically induced menopause
  - premenopausal amenorrhoea ≥6 months, (excl pregnancy)
- Body Mass Index <19kg/m^2
- Caucasian/Asian origin
- Current smoking
- ≥ 3 units alcohol daily
- Male hypogonadism

Predisposing medical conditions

- hyperthyroidism
- rheumatoid arthritis
- type 1 diabetes
- inflammatory bowel disease
- malabsorption/coeliac disease
- prolonged immobility
- organ transplantation
- hyperparathyroidism
- chronic liver disease

Drugs associated with increased fracture risk

- anticonvulsants
- antipsychotics
- Depo-Provera, >2yrs treatment
- excessive levothyroxine replacement therapy
- Lithium
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Aromatase inhibitors***** (see guidance below)
- GnRH analogues/ Androgen Deprivation Therapy (ADT)***** (see guidance below)
- Proton Pump Inhibitors
- Pioglitazone

*** Aromatase inhibitors (AI) and Androgen Deprivation Therapy (ADT)**

See Bone health in cancer patients: ESMO Clinical Practice Guidelines and algorithm in appendix 1[1,2]

Patients with cancer receiving chronic endocrine treatment known to accelerate bone loss should have a DEXA scan performed at baseline. Treat in conjunction with oncology specialist advice.

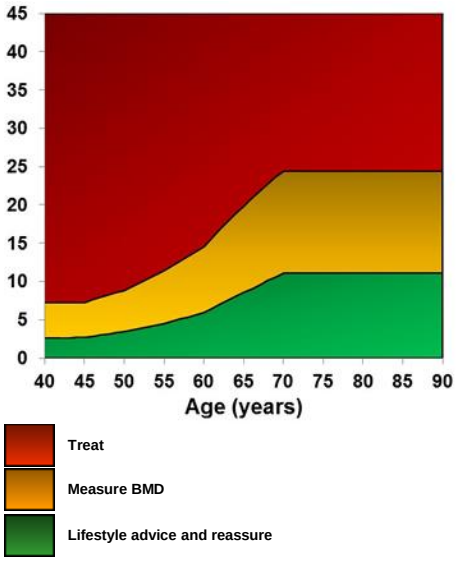
Assessment of Fracture Risk using FRAX®

The FRAX® tool is an algorithm which calculates a 10 year fracture probability **for people aged between 40 and 90 years** either with or without BMD values.

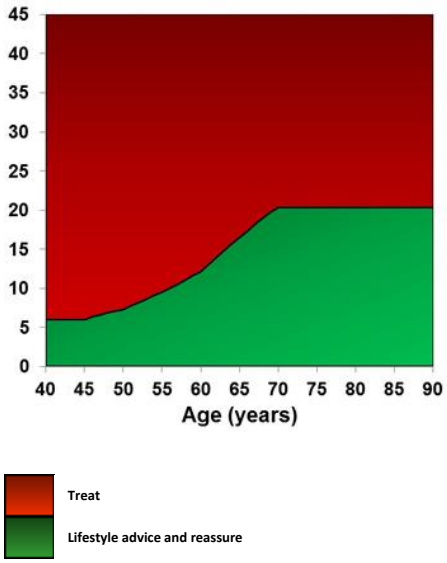
10 year probability of major osteoporotic fracture (%)

(Measurement of Bone Mineral Density helps to inform whether treatment is recommended)

Assessment without BMD



Assessment with BMD



See

a) www.shef.ac.uk/FRAX and the links to guidance published by the National Osteoporosis Guideline Group (NOGG)[3] for the management of osteoporosis.

b) NICE CG 146 Osteoporosis: assessing the risk of fragility fracture[4]

c) Interpretation and Use of FRAX in Clinical Practice[5]

Anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D[3]

	Vertebral	Non-vertebral	Hip
Alendronate	**A**	**A**	**A**
Ibandronate[a]	**A**	**A***	**NAE**
Risedronate	**A**	**A**	**A**
Zoledronic Acid	**A**	**A**	**A**
Calcitriol	**A**	**NAE**	**NAE**
Denosumab	**A**	**A**	**A**
HRT	**A**	**A**	**A**
Raloxifene	**A**	**NAE**	**NAE**
Teriparatide	**A**	**A**	**NAE**

A: grade A recommendation
* in subsets of patients only (post-hoc analysis
NAE: Not adequately evaluated
HRT: hormone replacement therapy
[a] Injection only available on Formulary

Therapeutic Agents Available For The Management Of Osteoporosis

***(See Table on page 3 for anti-fracture efficacy of therapies available*)**

Refer to the latest data sheet for full prescribing details about use in elderly, renal and hepatic impairment, contraindications, precautions etc.
Refer to the BNF- Guidance on prescribing in renal impairment- for advice on using eGFR / calculated creatinine clearance to adjust doses for patients with renal impairment.

Calcium and Vitamin D_3

Adequate levels of calcium and vitamin D_3 (colecalciferol) are required to ensure optimum effects of all the treatments for osteoporosis (see link to dietary calcium calculator)[6]. Unless the clinician is confident that the patient has adequate calcium intake and is vitamin D replete, calcium and colecalciferol supplementation at a dose of Calcium 1 – 1.2 gram (equivalent to 2.5 – 3.0g Calcium Carbonate) and colecalciferol 20 micrograms (800 units) daily should be prescribed. **Prescribe colecalciferol 800 units daily alone in patients with adequate calcium intake (approx. 1gram per day) who only need vitamin D supplementation.** If patient is vitamin D depleted (<25nmol/L) refer to guidelines on supplementation on Map of Medicine. Ensure repletion before starting treatment for osteoporosis.

Avoid colecalciferol in severe renal impairment as it cannot be converted to its active form in the renally impaired.

Bisphosphonates

- Alendronate (alendronic acid) is the first choice bisphosphonate for the majority of patients.
- Risedronate is recommended, in patients intolerant of alendronate, in young adults and in patients with glucocorticoid-induced osteoporosis where it may be advantageous due to rapid 'on/off' effect. Since the tablets are smaller, risedronate may also be considered for people who have difficulty swallowing alendronate.
- Intravenous bisphosphonates (e.g. Zoledronic acid) may be used under specialist guidance e.g. if oral bisphosphonates are not tolerated or there are compliance issues.
- Buffered effervescent alendronic acid (Binosto®) tablets may also be considered as an alternative in patients who have difficulty swallowing tablets. However this formulation is relatively high cost, and there is a lack of evidence to demonstrate improved tolerability/safety in patients with upper GI symptoms, thus parenteral options (including denosumab) are usually preferred.
- If patient is pre-menopausal or under 50 years old, seek specialist advice from rheumatologist.

Oral bisphosphonates should be swallowed whole with a glass of water 30-60 minutes before the first food or drink (other than water) of the day. Patients should stand or sit upright (not lie down) for at least 30 minutes post dose.
Discontinue treatment if oesophageal ulceration, erosion, stricture, or other severe gastrointestinal symptoms occur.

Bisphosphonates should be avoided in patients with moderate to severe renal impairment.

(eGFR < 35ml/min/1.73m^2 for alendronate, < 30ml/min/1.73m^2 for risedronate and Calculated Creatinine Clearance < 35ml/min for zoledronic acid)

Atypical femoral fractures (often bilateral) have been reported rarely with bisphosphonate therapy[7,8], mainly in patients receiving long-term treatment for osteoporosis. Patients should be advised to report any unexpected thigh, hip or groin pain. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated. (Refer to orthopaedics if necessary). For general advice on duration of therapy see page 7 of these guidelines.

Osteonecrosis of the jaw (ONJ) has been reported rarely with IV bisphosphonate use and very rarely with oral use[9]. Adequate oral hygiene should be maintained during and after bisphosphonate treatment. In patients with concomitant risk factors e.g. cancer, chemotherapy treatment, glucocorticoid treatment, or poor oral hygiene. Remedial dental work should ideally be completed before starting bisphosphonates. Any invasive dental work undertaken whilst taking bisphosphonates will require closer monitoring of the healing process.

Osteonecrosis of the external auditory canal has been very rarely reported[10] with both oral and IV bisphosphonates, mainly in association with therapy of 2 years or longer, with or without additional risk factors e.g. steroid use, chemotherapy, infection, or ear operation. Patients should be advised to report any ear symptoms whilst on bisphosphonate therapy.

Denosumab

Indicated for:-

1) Treatment of osteoporosis when bisphosphonates inappropriate, or if a fracture sustained whilst on bisphosphonate therapy for more than a year, in:
   a) Postmenopausal women
   b) Men at increased risk of fractures
2) Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, when bisphosphonates inappropriate.
3) Treatment of bone loss associated with long term glucocorticoid therapy in adult patients at increased risk of fracture where bisphosphonates inappropriate.

- Hypocalcaemia is a **contraindication** to denosumab therapy. Check serum calcium and correct pre-existing hypocalcaemia before initiating denosumab and before each dose.
- Ensure adequate intake of calcium and vitamin D (see link to dietary calcium calculator)[6] in all patients receiving denosumab (unless hypercalcaemic) [11].

- Administered as a 60mg subcutaneous injection (at any time of day) at 6 month intervals. May be initiated in primary care. Hospital to inform GP of the date of administration of denosumab injection if started as inpatient, and GP to set up a recall for future doses at 6 month intervals, to add denosumab to patient's repeat prescription and to remove other osteoporosis treatments (e.g. bisphosphonates). (*Guidance on set up of recall systems available from Medicines Management Team).*

- No dose adjustment required in patients with renal impairment, but check renal function prior to each dose to identify those that may be predisposed to hypocalcaemia. For patients predisposed to hypocalcaemia [e.g. severe renal impairment (creatinine clearance < 30ml/min; eGFR 15 – 29ml/min/1.73m^2) or on dialysis] recheck serum calcium within two weeks and 3 months after each dose or more frequently if clinically indicated[12]. Note that denosumab should only be used in patients with severe renal impairment under specialist supervision.

Osteonecrosis of the jaw (ONJ)[12] has been reported (rarely) in patients receiving denosumab for osteoporosis (most cases occur in cancer patients prescribed the 120mg dose). Give patient the **Denosumab Patient Reminder Card[13] which contains advice about ONJ.** Patients should avoid invasive dental procedures during treatment if possible. Regular dental check-ups are recommended in patients on denosumab. If invasive dental work is undertaken whilst the patient is on denosumab therapy, closer monitoring of the healing process will be necessary.

Atypical femoral fractures have been reported rarely during long-term (≥2.5 years) treatment[14]. Any patient presenting with unexpected thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated. (Refer to orthopaedics if necessary).

Osteonecrosis of the external auditory canal has been very rarely reported with denosumab and should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma.[15] Possible risk factors include steroid use, chemotherapy, infection and trauma. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.

Be aware that bone loss is rapid on discontinuation of denosumab therapy, therefore a 'drug holiday' is not appropriate. Consider continuing denosumab long term in those with previous hip or vertebral fractures.

If/when cessation of denosumab is indicated it should be followed by further anti-resorptive therapy to prevent bone loss. Seek specialist advice for current policy.

Raloxifene

Selective oestrogen receptor modulator (SERM)

For postmenopausal women with vertebral osteoporosis, with an unsatisfactory response to or an intolerance of bisphosphonates. **Avoid in severe renal impairment (eGFR<30ml/min/1.73m^2), or if there is a (family) history of venous thromboembolic disease.**

Teriparatide injection (Specialist Use only)

Indications restricted to patients with an unsatisfactory response/intolerance to the above therapies **and**

- aged ≥ 65 yrs old who have a T score of –4 SD or below **or**
- aged ≥ 65 yrs old who have a T score of -3.5 SD or below **plus** at least 2 fractures **or**
- aged 55 – 64 yrs old who have a T score of -4 SD or below **plus** at least 2 fractures

Use with caution in moderate renal impairment (eGFR between 30 and 50ml/min/1.73m^2). Contraindicated in severe renal impairment (eGFR<30ml/min/1.73m^2.

Hormone Replacement Therapy

Recommended as treatment for the prevention of osteoporosis in women with a premature menopause (up to 50 years of age).

Combination Therapy

(not including combinations with Calcium and colecalciferol)

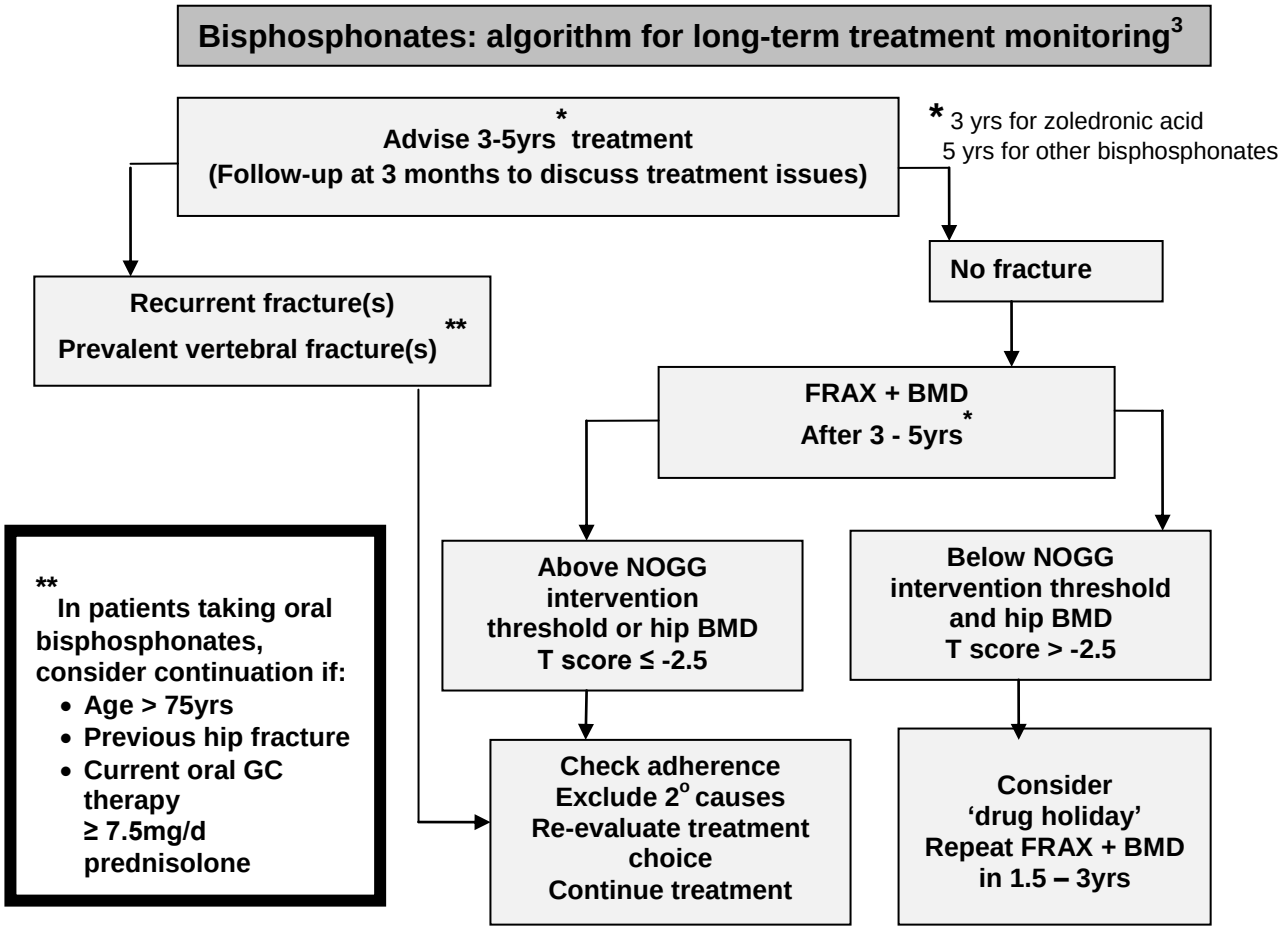
- is not routinely prescribed but may be rarely used under specialist recommendation

Duration Of Treatment

Review and reassess all patient's fracture risk at intervals during treatment (use FRAX® +/- DXA). Ensure patient is calcium and vitamin D replete (see link to dietary calcium calculator)[6], or continue adequate supplementation).

Oral bisphosphonates – review after 5 years and follow the algorithm below:

(additional information available for oral bisphosphonates on pages 17-19 in the NOGG guideline NOGG Clinical Guideline for prevention and treatment of Osteoporosis)[3]



Denosumab –Denosumab for the treatment of osteoporosis and has trial evidence up to 10 years with substantial reductions in fracture risk and increases in bone mineral density, twice as great than seen with bisphosphonates.

However, stopping denosumab results in rapid loss in bone density and an increased risk of vertebral fractures. All of the increase in hip bone density is lost by 12 months[16,17]. This is associated with a 30% increased risk of multiple vertebral fractures compared with placebo[18]. The increase in risk may occur as early as three months after a missed injection and mostly reflects the high baseline fracture risk. Oral or intravenous bisphosphonate may not protect against this bone loss.

For this reason, patients should complete at least 10-years of denosumab therapy. If patients discontinue denosumab, due to falling renal function below a creatinine clearance of 25ml/min or other reasons, this should be discussed with clinicians with expertise in osteoporosis. Strategies are being developed for those who need to stop.

Raloxifene– review and reassess after up to five years of treatment and continue if indicated.

Teriparatide should be used for a maximum of 24 months only.

Zoledronic acid – review after 3 years and follow the algorithm on page 8: (additional information available for zoledronic acid on pages 17-19 in the NOGG guideline NOGG Clinical Guideline for prevention and treatment of Osteoporosis)[3]

Note: in patients who remain at high risk of fracture, then the expectation is that treatment will continue in some form.

References

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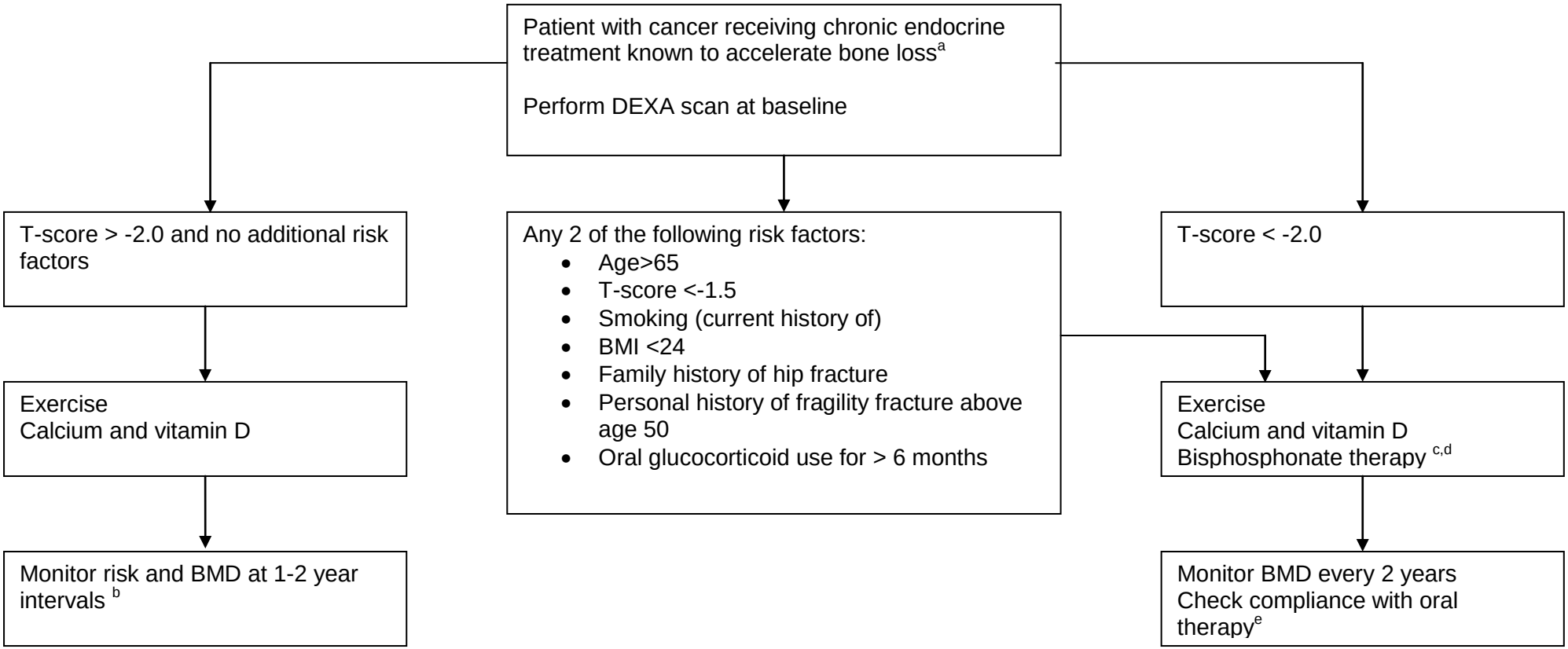
Approved by:	**Basingstoke Southampton and Winchester District Prescribing Committee** **Date : October 2019 Review Date : October 2021**

Appendix 1 – Treatment algorithm for the prevention of bone loss for women with breast cancer receiving an aromatase inhibitor or ovarian suppression and men with prostate cancer undergoing androgen deprivation therapy. Adapted from Bone health in cancer patients: ESMO Clinical Practice Guidelines. [2]



Recommended algorithm for managing bone health during cancer treatment
[a] Includes aromatase inhibitors and ovarian suppression therapy/oophorectomy for breast cancer and androgen deprivation therapy for prostate cancer.
[b] If patients experience an annual decrease in BMD of ≥ 10% (or ≥ 4%-5% in patients who were osteopaenic at baseline) using the same DEXA machine, secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. Use lowest T-score from spine and hip.
[c] Six monthly i.v. zoledronic acid, weekly oral alendronate or risedronate acceptable.
[d] Denosumab may be a potential treatment option in some patients.
[e] Although osteonecrosis of the jaw is a very rare event with bone protection doses of antiresorptives, regular dental care and attention to oral health is advisable.
BMD – Bone mineral density
BMI – Body mass index