Trust Guideline for the Management of: Osteoporosis, Secondary Prevention of Fracture in Post-Menopausal Women

Document Control:

For Use In:	Postmenopausal women who have prior history of low trauma skeletal fractures By: Clinicians who practice in the osteoporosis field (primarily endocrinologists, rheumatologists, orthopaedic surgeons and Older People's Medicine (OPM) physicians) For: The secondary prevention of skeletal fractures in women who are known to have osteoporosis or who are at elevated fracture risk		
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Version	Date	Author	Reason/Change
V3.0	06/02/2020	Professor Jeremy Turner	Partial re-write
V4.0	06/02/2024	Smriti Gaur	Partial re-write. Addition of Romososumab.

Previous Titles for this Document:

Previous Title/Amalgamated Titles	Date Revised
None	Not applicable

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:

- Endocrinology Consultants
- Rheumatology Consultants
- Geriatric and Orthogeriatric consultants

Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline applicable to Norfolk and Norwich University Hospitals NHS Foundation Trust; please refer to local Trust's procedural documents for further guidance.

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Quick Reference Guide

1. Introduction

1.1. Rationale

There have been significant updates to several pieces of major national osteoporosis guidance since the last Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH) osteoporosis clinical guidelines were written. Specifically, National Osteoporosis Guideline Group (NOGG) guideline was updated in 2021 and a major new National Institute for Health and Care Excellence (NICE) document has been released (TA791). There have also been other important changes in the field including drugs coming off patent (Teriparatide, rhPTH1-34) and changes in thinking about recommended duration of treatment, especially with respect to the bisphosphonates.

The National Institute for Health and Care Excellence (NICE) CG146, Osteoporosis, Assessing the risk of fragility fracture

NICE TA464, Bisphosphonates for treating osteoporosis

NICE TA161, secondary prevention of fracture:

NICE TA204, Denosumab

NICE TA791, Romosozumab

1.2. Objective

The objective of this clinical guidelines is to:

- provide guidance on the secondary prevention of low energy fracture in post-menopausal women with known or suspected osteoporosis.
- standardise and unify this aspect of osteoporosis management throughout the NNUH.
- provide clear, evidence based, up to date guidance on osteoporosis management and secondary fracture prevention.
- reflect and incorporate current national guidance from opinion-leading bodies such as NICE and NOGG in osteoporosis management but also to provide guidance on the use of newer agents such as rhPTH1-34, Parathyroid hormone (PTH), denosumab and romosozumab.
- reflect newer thinking in the osteoporosis world that has become more widely accepted since some of the existing guidance was written covering issues such as duration of treatment, role of repeat Dual Energy X-ray absorptiometry (DEXA) scanning, use of bone turnover marker blood tests and the risks/side effects of osteoporosis drugs, especially the bisphosphonates, such as atypical femoral fracture.

1.3. Scope

Secondary prevention of low-energy fractures in postmenopausal women who are either diagnosed with or suspected to have osteoporosis. It is recommended that the guidance in this document is not used for managing osteoporosis in men or women who are pre-menopausal.

1.4. Glossary

The following terms and abbreviations have been used within this document:

Term	Definition
ONJ	Osteonecrosis of the jaw
NOGG	National Osteoporosis Guideline Group
DEXA	Dual Energy X-ray absorptiometry
FRAX	online fracture risk calculator
NOS	National Osteoporosis society
CTX	C terminal telopeptide / carboxy terminal collagen cross links
BMD	Bone mineral density
PTH	Parathyroid hormone
MOF	Major osteoporotic fracture

2. Responsibilities

Doctors and allied health professionals working in the osteoporosis field (primarily endocrinologists, rheumatologists, orthogeriatricians and Older People's Medicine (OPM) physicians) should be aware of the contents of this guideline and arrange for the investigation and subsequent management of osteoporotic fracture in post-menopausal women accordingly.

During its development the guideline has been circulated for comment to directorates of endocrinology, rheumatology, older people's medicine and orthogeriatricians.

3. Processes to be followed

Please refer to the "Quick reference guide" in which the suggested pathway for treatment of post-menopausal female patients with a low energy fracture history is outlined. This includes advice on whether or not a DEXA scan is required, how to interpret the latter, when to initiate treatment and with what agent. It furthermore recommends suitable treatment duration and when to consider referral to a specialist clinic.

The structure of the treatment pathway has, in essence, 3 components:

- Assessment of whether or not secondary prevention by pharmacological means is indicated. For all where there is a clear history of low energy impact and the patient is more than 75 years of age then pharmacological intervention will be indicated and in the majority of such cases, treatment can be started without DEXA scanning. There are a number of circumstances where DEXA scanning is indicated and these are specified in the quick reference guide on page 4.
- The second part is based on use of low acquisition cost, high efficacy, evidence based, orally active bisphosphonates such as weekly alendronic acid, for a limited time frame (5 – 7 years in the majority of cases).
- The patient should only progress to the third part of the pathway if they have true intolerance of oral bisphosphonate therapy or if they sustain a fracture

while on treatment (fractures sustained very early on during a course of treatment e.g. within the first 12-18 months should attract less attention).

The pathway should then involve referral to a specialist clinic, where further investigations will be performed, and treatment will be escalated as set out in the quick reference guide pathway above. A parenteral bisphosphonate will usually be the first choice in the specialist clinic, but other possibilities include denosumab and, after a fracture on treatment, anabolic agents such as rhPTH1-34 will be considered.

There are several key aspects of this guidance that we would draw the reader's attention to:

1. If there is a clear low trauma history to the index fracture and the patient is more than 75 years of age then we recommend commencing the secondary prevention pathway without recourse to DEXA scanning. This is in keeping with guidance in NICE TA464 and reflects the high likelihood of established osteoporosis being present in such patients.
2. If DEXA scanning is performed and the T score is -2.5 or lower, in the presence of appropriate fracture history, this should trigger automatic initiation of bone protection.
3. Bone Mineral density (BMD) is only 1 of several risk factors for fracture, we therefore recommend that if DEXA scanning is performed and the T score is above -2.5, the results of DEXA are integrated with other risk factors in order to predict a 10 year fracture risk, using the FRAX risk calculator available on the University of Sheffield web pages.

This is analogous to the Q-RISK cardiovascular risk calculators available online with which many colleagues are familiar. FRAX also provides advice on whether or not to recommend pharmacologic intervention based on NOGG guidance and for each FRAX calculation that is performed, a link is provided to individualised "treat or not to treat" guidance according to the patient's 10 year fracture risk.

4. Repeat DEXA scanning is no longer considered to be necessary in routine cases to assess response to treatment and should not be used as a matter of course. Indeed improvements in BMD only account for approximately 50% of fracture risk reduction with bisphosphonates.

Re-scanning should however be considered if a patient sustains a low energy fracture while on treatment (unless very early during the treatment pathway), if they sustain a low energy fracture after a course of treatment has been completed, or by a specialist upon referral to a specialist osteoporosis clinic.

Re-scanning at intervals of less than 3 years is usually contra-indicated as the magnitude of bisphosphonate effect on BMD within this time frame is often smaller than the Coefficient of variance (CV) of the measurement on most densitometers.

5. A course of bisphosphonate treatment should not be considered to be open-ended or completely risk-free. Patients on bisphosphonates are at elevated (albeit small) risk of atypical femoral fractures and osteonecrosis of the jaw (ONJ). Other potential risks associated with bisphosphonates are starting to emerge (e.g. possible elevated carcinoma of the oesophagus risk with oral

bisphosphonates, although the effect size and strength of association are still unknown).

It is therefore important that benefit outweighs risk and therefore duration of treatment of 5 - 7 years is recommended in most cases. Case-specific factors should however be included in decision making around individual circumstances.

6. Interpretation of C terminal telopeptide (CTX) results: To assess compliance with and efficacy of bisphosphonate therapy, the guideline recommends routinely checking the plasma CTX level after the first 4 months of bisphosphonate therapy. If the drug is being taken and absorbed then a significant suppression of CTX level will be observed confirming that bone resorption is being effectively suppressed. Level less than 0.3 microgram/L indicates effective treatment. This is considered to be a quicker, more reliable, and more cost-effective way of assessing treatment efficacy than is waiting 3 years to perform a repeat DEXA scan.
7. There is evidence that HRT decreases the risk of spine, hip, and other osteoporotic fractures, even in women at low risk as well as in those with established osteoporosis (Reference 9). HRT use in the early postmenopausal years can offer long lasting benefits for prevention of postmenopausal bone loss and fracture prevention. Hence consideration should be given to the use of HRT in women, aged 60 or <10 years past menopause, with a low baseline risk for adverse events. As with all agents, careful consideration of the risk benefit ratio needs to be undertaken.

HRT remains an option for osteoporosis treatment and fracture prevention in women who have undergone premature ovarian failure or surgically induced menopause. Further guidance is available from the Royal Osteoporosis Society. Similarly, a limited role also exists for the use of the selective oestrogen receptor modulator drug Raloxifene as outlined in TA161(https://www.nice.org.uk/Guidance/TA161)

8. There is growing awareness that at the end of a course of Denosumab therapy many patients exhibit a rebound fall in BMD due to marked increase in bone turnover within 6–24 months of discontinuation, which is associated with a concomitant increase in fracture risk (up to 7 fold) (reference 11). There is no definitive evidence on how best to manage this challenge but one possible way to handle this situation based on currently available evidence is to administer two sequential zoledronate infusions within the first 12 months after the end of the course of Denosumab (reference 12)
9. Romosozumab is a humanised monoclonal antibody that has been approved for the treatment of severe osteoporosis in postmenopausal women who are at a very high risk of fracture (TA791). It has been observed that after completing a course of Romosozumab therapy, there is an increase in bone turnover, which can lead to a rebound fall in BMD in many patients, and this is associated with a higher risk of fracture (reference 14). To maintain the beneficial skeletal effects of Romosozumab, it is recommended to administer one sequential Zoledronate infusion within the first 12 months after the completion of Romosozumab therapy. (reference 14). It is essential that

patient is supplemented with adequate calcium and vitamin D before and during the treatment.

10. Note on management of fracture risk in steroid treated patients: These comments pertain to those on 7.5 mg/day or more of prednisolone (or equivalent doses of other glucocorticoid) for 3 months or more. It should be borne in mind that a higher T score cut off is conventionally employed for marking out high fracture risk individuals on steroids and conventionally T < -1.5 is considered significant in this context. However, fracture risk is thought to abate quite rapidly upon cessation of steroid therapy if this possible.

The greatest evidence base for managing fracture risk in steroid treated patients relates to the use of bisphosphonates, however, there is also an evidence base supporting the use of rhPTH1-34 in this situation (reference 13) and especially now that generic rhPTH1-34 is available this option should be considered where bisphosphonates have been unsuccessful or are contraindicated.

11. Teriparatide is a recombinant human parathyroid hormone analogue. It increase osteoblast formation and reduced osteoblast apoptosis which results in an increase in bone turnover and formation. Procollagen 1 Intact N-Terminal Propeptide (P1NP) is bone marker that can be used to assess the response to teriparatide. Quantifying PINP measures anabolic activity in the bone and an increase in P1NP would be expected in patients on Teriparatide. Hence PINP monitoring may be useful for clinicians prescribing teriparatide for osteoporosis patients at high risk for fracture. (Reference 16)

4. References

1. FRAX: http://www.shef.ac.uk/FRAX/tool.jsp?country=1
2. NOGG: NOGG guidance 2017
3. NICE CG146, Osteoporosis, Assessing the risk of fragility fracture
4. NICE TA464, Bisphosphonates for treating osteoporosis
5. NICE TA161, secondary prevention of fracture:
6. NICE TA204, Denosumab
7. NICE TA791, Romosozumab
8. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ; AMG 162 Bone Loss Study Group. N Engl J Med. 2006 Feb 23;354(8):821-31. Denosumab in postmenopausal women with low bone mineral density.
9. BMS-Consensus Statement- prevention and treatment of osteoporosis in Women- Sept 2023
10. Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, de Papp A, Bauer DC; Fracture Intervention Trial Steering Committee; HORIZON Pivotal Fracture Trial Steering Committee. N Engl J Med. 2010 May 13;362(19):1761-71Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur.

11. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guañabens N, Obermayer-Pietsch B, Ralston SH, Eastell R. Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.08.003.
12. Bente Langdahl et al. Abstract LB-1169. JBMR 2019. Vol 34, S1
13. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007;357(20):2028–2039.
14. McClung, M.R., Brown, J.P., Diez-Perez, A., Resch, H., Caminis, J., Meisner, P., Bolognese, M.A., Goemaere, S., Bone, H.G., Zanchetta, J.R., Maddox, J., Bray, S. and Grauer, A. (2018), 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, 33: 1397-1406. https://doi.org/10.1002/jbmr.3452
15. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment:

    Report of a Task Force of the American Society for Bone and Mineral Research. Robert A Adler et al Journal of Bone and Mineral Research, Vol. 31, No. 1, January 2016, pp 16–35 DOI: 10.1002/jbmr.2708
16. Krege JH, Lane NE, Harris JM, Miller PD. PINP as a biological response marker during teriparatide treatment for osteoporosis. Osteoporos Int. 2014 Sep;25(9):2159-71. doi: 10.1007/s00198-014-2646-0. Epub 2014 Mar 6. PMID: 24599274; PMCID: PMC4134485.

5. Monitoring Compliance

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
Incidents around bisphosphonate duration and DEXA scan frequency and bone marker monitoring while on treatment	Datix	Clinical Governance Lead for Endocrinology	Clinical Governance Lead for Endocrinology	6 monthly

We suggest that compliance with the guideline in respect of parameters such as 10-year maximum bisphosphonate duration, absence of routine repeat DEXA scanning, 12 month CTX assessment and use of second line agents only where strictly indicated by the guideline be audited. We suggest a 90% adherence standard.

6. Appendices

6.1. Appendix 1 - Additional information regarding the use of Teriparatide in managing osteoporosis in post-menopausal women.

Teriparatide:

In keeping with NICE guidance, teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to take alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate or who have had an unsatisfactory response to treatment with alendronate or risedronate and
- who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.

For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

For the purposes of this guidance, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly. For the purposes of this guidance, an unsatisfactory response is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.

6.2. Appendix 2 - Additional information regarding the use of Romosozumab in managing osteoporosis in post-menopausal women.

Romosozumab

NICE recommends romosozumab as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if they have had a major osteoporotic fracture (MOF) within 24 months (so are at imminent risk of another fracture) and the manufacturing company provides romosozumab according to the commercial arrangement.

According to NICE, a MOF is defined as a fragility fracture of the spine, hip, forearm, or humerus as per the submission from the manufacturing company.

For the purpose of this guidance, in exceptional circumstances, where patient has post-menopausal osteoporosis with a BMD T score of <-4.0 (at the hip or spine) or BMD T-score of <-3.5(at the hip or spine) and more than 2 osteoporotic vertebral fractures, an earlier intervention with Romosozumab can be considered after a discussion in ERBON – Rare Bone Network.

Romosozumab requires GP referral to secondary care specialist OP clinic. It should only be initiated in secondary care.

Risk Assessment

For the purpose of this guidance, cardiovascular risk must be assessed using Q-RISK 3 score prior to commencement of Romosozumab.

Do not start Romosozumab if:

- There is previous history of Myocardial infarction (MI) or Cerebrovascular accident (CVA) **or**
- QRISK3 Relative Risk is >1 **or**
- The patient, after seeing their absolute and relative risk of MI or CVA on QRISK3 does not want to proceed with the therapy.
- Romosozumab must be discontinued if patient experiences MI or CVA during treatment.

7. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	Medical	**Department**	Endocrinology
Name of person completing form	Dr Smriti Gaur	**Date**	

Equality Area	**Potential Negative Impact**	**Impact Positive Impact**	**Which groups are affected**	**Full Impact Assessment Required YES/NO**
Race	No	No	None	No
Pregnancy & Maternity	No	No	None	No
Disability	No	No	None	No
Religion and beliefs	No	No	None	No
Sex	No	Yes	Post menopausal women	No
Gender reassignment	No	No	None	No
Sexual Orientation	No	No	None	No
Age	No	Yes	Post menopausal women	No
Marriage & Civil Partnership	No	No	None	No
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?				

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.