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TECHNICAL
REPORT

Postmenopausal osteoporosis management

A review of the evidence to inform the development of quality indicators

Annalijn Conklin, Ohid Yaqub, Claire Celia, Ellen Nolte

Prepared for Amgen

RAND EUROPE

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Preface

This document provides Amgen with a report presenting a comprehensive review of reviews as identified from the peer-reviewed and grey literature regarding the screening and diagnosis of osteoporosis and related risk factors and the prevention and treatment of osteoporosis and osteoporosis-related fractures. Secondly, we carried out case study reviews of current practices for managing postmenopausal osteoporosis in England, France, Germany and Spain, with a particular focus on the quality of care provided to those with osteoporosis and associated fractures. This work aims to inform the development of quality indicators for postmenopausal osteoporosis management in Europe.

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Summary

Osteoporosis is the most common clinical disorder of bone metabolism. It is characterised by low bone mass and microarchitectural deterioration of bone tissue and consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity; clinical complications include disability and chronic pain. It is estimated that in developed countries around 50 percent of women aged 50 and older will sustain an osteoporotic fracture during their lifetime.

Whilst there is accumulating evidence on approaches to the management of osteoporosis, the overall evidence as to the most effective interventions for the prevention and treatment of osteoporosis and associated fractures remains mixed. There is a need to draw together the available evidence to ensure high quality services are provided to those at risk of developing the condition and associated fractures.

This report aims to inform the development of quality indicators for postmenopausal osteoporosis management through (a) assessing the evidence for screening and diagnosis of osteoporosis and related risk factors, and for prevention and treatment of osteoporosis and osteoporosis-related fractures; (b) describing current practice for managing postmenopausal osteoporosis in Europe; and (c) highlighting existing gaps in the evidence base and management practices in Europe.

We have undertaken two separate sets of analyses. These involved, first, a comprehensive review of reviews as identified from the peer-reviewed and grey literature regarding the screening and diagnosis of osteoporosis and related risk factors and the prevention and treatment of osteoporosis and osteoporosis-related fractures. Secondly, we carried out case study reviews of current practices for managing postmenopausal osteoporosis in England, France, Germany and Spain, with a particular focus on the quality of care provided to those with osteoporosis and associated fractures.

There is good evidence on the effects of selected treatments on clinical outcomes of postmenopausal osteoporosis and associated fractures

Our review of reviews identified a well developed evidence base on the effects of selected treatments on clinical outcomes of postmenopausal osteoporosis and associated fractures, and on the usefulness of selected simple risk factor assessment tools to identify postmenopausal women who would benefit from further diagnostic assessment, such as dual-energy x-ray absorptiometry (DXA) measurement. We acknowledge the limitations of a review of reviews, most importantly the failure to consider more recent original studies that have not yet been included in reviews but which may be relevant and important, as for example emerging evidence examining a possible association between bisphosphonate use

and atypical fractures. Beyond this limitation, it is fair to conclude that considerable uncertainties remain in the evidence base: the optimal use (frequency, quantity, duration) of pharmacological interventions for preventive purposes; the combinations of pharmacological and/or non-pharmacological interventions that may prevent any particular type of fracture; identifying specific populations who might benefit from a given intervention (including populations who have hitherto not been studied); and the effectiveness of population-based screening. In spite of these uncertainties, the available evidence does provide some basis to inform quality improvement in clinical practice, underpinning the development of clinical guidelines in many settings in Europe.

The evidence on current approaches and practices to managing postmenopausal osteoporosis in England, France, Germany and Spain is complex

All four countries under review have introduced national-level guidelines for the management of osteoporosis. The extent to which these are implemented and/or adhered to varies, determined, in great part, by whether diagnosis and/or treatment is being reimbursed under the statutory system as well as awareness of the guidance among professionals concerned with the management of the condition.

In all countries reviewed here, there is evidence of under-diagnosis and of under-treatment, although this varies among countries, with Germany at one end of the spectrum with relatively low treatment rates (between one-fifth and one-quarter of potentially eligible women receiving treatment), and Spain at the other. Available literature points to a number of challenges faced by practitioners to implement guidance. These include lack of awareness of and knowledge about the condition, and of understanding of reimbursement mechanisms; uncertainty about responsibilities for management among providers; and restricted access to diagnostic equipment.

Improved information on reimbursement modalities and clarification of responsibilities for the management of osteoporosis and associated fractures and communication between sectors are likely to go some way to enable a more systematic approach to addressing the related societal burden in European populations.

There is considerable need for the better understanding of current approaches and practices to managing postmenopausal osteoporosis

Observations made in this study had to draw, to considerable extent, on a rather patchy evidence base, often relying on studies of small samples and/or single providers and with little systematic data collection. Furthermore, evidence that is available frequently relates to data collected in the early 2000s, so findings reported here have to be interpreted with caution.

We have identified a particular need for the establishment of routine monitoring systems to enable better understanding of contemporary patterns and trends and identify care gaps in the management of postmenopausal osteoporosis and associated fractures. Such analyses are crucial to inform targeted strategies and policies to effectively address the burden of osteoporosis and associated fractures, which is sizable and set to increase across Europe.

The systematic use of quality indicators can provide a means to enable tracking care quality. We set out considerations as a starting point for the further development of quality measures for postmenopausal osteoporosis in Europe. Such development might be able to draw, to considerable extent, on experiences in the United States, where a small set of

indicators related to the testing and the management of osteoporosis in women are already being used routinely to monitor the quality of care provided to older patients.

Acknowledgements

We gratefully acknowledge the very helpful guidance provided by Charlotte Paddison in developing the search strategy for the review of reviews of the evidence on the diagnosis, prevention and treatment of postmenopausal osteoporosis. We are also very grateful to Tom Ling and Anas El Turabi for their very insightful comments and suggestions provided on an earlier draft of this report. We are also indebted to Jiri Skoupy for administrative support. We would further like to thank Enkhe Badamgarav of Amgen for her continuous support and interest in discussing the ideas and concepts that led to this report.

The views expressed in this report are those of the authors alone and do not necessarily represent those of Amgen. The authors are fully responsible for any errors.

CHAPTER 1 Introduction

1.1 Context

Osteoporosis is the most common clinical disorder of bone metabolism. It is characterised by low bone mass and microarchitectural deterioration of bone tissue and consequent increase in bone fragility and susceptibility to fracture.[1] Osteoporotic fractures are a major cause of morbidity; clinical complications include disability and chronic pain. It is estimated that in developed countries around 50 percent of women aged 50 and older will sustain an osteoporotic fracture during their lifetime.[2-3]

Osteoporotic fractures place a high burden on populations; it has been estimated that in the European Union there are about 1,700 associated fractures per day (about 650,000/year).[4] Osteoporosis and consequent fractures are associated with increased mortality, with for example over 1 percent of all deaths in Sweden attributed to hip fractures.[5] Relative to other chronic conditions, the burden associated with osteoporosis as measured by disability-adjusted life-years (DALYs) has been shown to be greater than that associated with rheumatoid arthritis, asthma or hypertensive heart disease but lower than that attributed to ischaemic heart disease, chronic obstructive pulmonary disease (COPD) or Alzheimer's disease.[6]

The direct costs attributed to osteoporotic fractures in Europe in 2000 were estimated at €36 billion,[7] with estimates for the United States placing the direct medical costs associated with osteoporosis at annually $17–20 billion (€12–15 billion).[8] Based on the expected demographic profile of the population in Europe, Kanis and Johnell (2005) projected the direct costs attributable to osteoporotic fractures to rise to €57.8 billion in 2050.[7] These figures however underestimate the 'true' societal and personal costs associated with osteoporosis. This is because of uncertainty about the 'true' burden related to osteoporosis; diagnosis relies on the quantitative assessment of bone mineral density (BMD) with different techniques producing different estimates of risk, depending on type of fracture and skeletal site examined.[2]

The management of osteoporosis can be distinguished into measures aimed at reducing the risk of developing osteoporosis and those aimed at strengthening bone quality and preventing further bone loss to reduce the risk of initial or subsequent fracture in those who have already have been diagnosed with low BMD or fractures. Measures aimed at reducing the risk for developing osteoporosis tend to focus on promoting healthy lifestyles, including physical activity and weight training, diets that provide for adequate intake of calcium and vitamin D, and avoidance of modifiable risk factors such as smoking.[4] Pharmacological interventions are generally aimed at the treatment of postmenopausal

osteoporosis and for the prevention of fractures. The overall evidence as to the most effective interventions for the prevention and treatment of osteoporosis remains mixed. There is a need to draw together the available evidence to ensure there is a high quality of services for those at risk of developing the condition and those with the condition and associated fractures.

This report aims to inform the development of quality indicators for postmenopausal osteoporosis management through reviewing the evidence base for the management of postmenopausal osteoporosis in Europe. Specifically, it aims to:

(i) assess the evidence for the screening and diagnosis of osteoporosis and related risk factors and for the prevention and treatment of osteoporosis and osteoporosis-related fractures

(ii) describe current practice for managing postmenopausal osteoporosis in Europe

(iii) highlight existing gaps in the evidence base and management practices in Europe.

1.2 Our approach

To meet the objectives set out above, we have undertaken two separate sets of analyses. These involved, first, a comprehensive review of reviews as identified from the peer-reviewed and grey literature for the screening and diagnosis of osteoporosis and related risk factors and for the prevention and treatment of osteoporosis and osteoporosis-related fractures. The review is described in Part I of this report, setting out the methods employed, the key findings and observations emerging from the analysis. Second, we carried out a review of current practices to managing postmenopausal osteoporosis in selected countries in Europe, focusing on four areas: (a) national strategies to managing osteoporosis in postmenopausal women; (b) guidelines in place and evidence of their use; (c) uptake of preventive and therapeutic interventions; and (d) the quality of care for those with osteoporosis and osteoporosis-related fractures. This analysis was carried out by means of selected country case studies; our approach and main observations are set out in Part II of this report. Part III brings the main findings of the two sets of analyses together and embeds them into a broader discussion on the development and use of quality indicators for the management of postmenopausal osteoporosis in European settings.

Part I. The diagnosis, prevention and treatment of postmenopausal osteoporosis: a review of reviews

CHAPTER 2 The diagnosis, prevention and treatment of postmenopausal osteoporosis

This chapter reports on the comprehensive review of reviews as identified from the peer-reviewed and grey literature for the screening and diagnosis of osteoporosis and related risk factors and for the prevention and treatment of osteoporosis and osteoporosis-related fractures. We begin by outlining the methods used, and then provide an overview of the key findings. We conclude with a set of summary observations emerging from the review.

2.1 Methods

We performed an electronic search of bibliographic databases (Cochrane Library of Systematic Reviews and Controlled Trials, Centre for Research and Dissemination (CRD), PubMed and Embase) and targeted websites (Agency for Quality in Health Care and European Medicines Agency) to identify systematic reviews and/or meta-analyses of studies of the prevention and treatment of osteoporosis and osteoporosis-related fractures and the screening and diagnosis of osteoporosis and related risk factors among postmenopausal osteoporosis. We used a combination of free-text and thesaurus terms for 'postmenopausal', 'osteoporosis', 'prevention', 'treatment', 'systematic review' and 'meta-analysis'. Filters for publication type were used where relevant. No limitations were imposed on language or publication date. Searches were performed between March and May 2011.

Two reviewers (AC and OY) screened titles and abstracts of records for potential eligibility for inclusion. Primary studies (e.g. trials, observational studies), editorials and commentaries were excluded. Full texts were retrieved for all titles and abstracts deemed potentially eligible. Studies were included if they reported data for postmenopausal women and primary osteoporosis and some detail on the review methods (e.g. database, search date, strategy or quality assessment). Studies of steroid-induced osteoporosis, surgical postmenopausal osteoporosis, secondary osteoporosis, or other women patient groups with co-morbidities (e.g. breast cancer) were excluded because this group would require a separate evidence-based approach for the management of osteoporosis since co-morbidity profiles vary widely.[9] Disagreements about abstract and/or full-text eligibility were resolved by consensus and/or discussion with the senior investigator (EN).

Data were extracted using a standardised evidence table with the following a priori headings: retrieval source, authors, title, publication year, stated aim(s), intervention type, intervention goal, agents (e.g. bisphosphonates, vitamin D, calcium), review focus

(efficacy, effectiveness, economic), comparative (intra/inter intervention types), method (narrative/meta-analysis), search date and number of studies analysed, key findings, key words, outcome measure(s), authors' conclusions, and comments. For multiple publications on the same review or meta-analysis the most recent publication was used. Two reviewers (AC and OY) entered an equal share of eligible reviews; however, a quarter of eligible reviews were randomly selected for duplicated extraction to check for consistency (EN). Discrepancies were discussed resolved by consensus.

Studies included were assessed for quality, using a range of hierarchical criteria developed on the basis of criteria recommended by the Centre for Reviews and Dissemination.[10] We considered five criteria: inclusion/exclusion criteria are made explicit, adequacy of the search methodology, whether findings were synthesised, whether studied reviewed were quality assessed, and the level of detail provided on individual studies, operationalised to mean (a) clear definition of efficacy/effectiveness over, for example, study setting (e.g. 'real-world' effects) and (b) clear description of limitations (Table 2.1).

We distinguished mandatory and optional criteria; ratings on each criterion were assigned separately by two reviewers and then combined to arrive at an overall rating of 'very high quality' to 'low quality' or 'to be discarded'. Inter-rater agreement was found to be high on individual criteria (Kappa ranged from 0.962 on criterion 5a to 1.00 on criteria 3 and 5b), and on the overall quality rating (Kappa=0.976, $p<0.001$) (Table 2.1). Any disagreements were resolved by consensus and cross-checking the relevant full text prior to analysis.

Table 2.1 Review quality assessment criteria and Kappa scores

Quality criterion	Quality level					Kappa score
	Very high	High	Medium	Low	Discard	
*** Inclusion and exclusion criteria explicit** 0=no description; 1=one reported; 2=both reported	2	1 or 2	1 or 2	0	0	0.986
The search strategy was adequate						
** (a) Explicit search strategy* 0=none; 1=search terms and screening process reported; 2=diagram of search strategy	2	1 or 2	1	0	0	0.977
(b) Number of databases searched	3+	(b) or (c) is reported	At least two of (b), (c) or (d) are reported	At least one of (b), (c) or (d) is reported	0	0.988
(c) Number of languages included 0=not reported; multiple=no limit	2+				0	0.978
(d) Dates searched 0=not reported; 1=reported	1	1			0	0.970
Results were synthesised 0=no; 1=yes	1	1	0 or 1	0	0	1.00
*** The quality of the included studies was assessed** 0=no; 1=yes	1	1	1	0	0	0.984
Individual studies included were presented in sufficient detail						
(a) Efficacy and effectiveness clearly defined 0=none; 1=either; 2=both	1 or 2	1 or 2	(a) or (b) are reported	0	0	0.962
(b) Review limitations clearly described 0=no; 1=yes	1	1		0	0	1.00

NOTE: *criterion considered mandatory

2.2 Results

The search retrieved 2,574 citations of which 211 were identified as potentially eligible after removal of duplicates and initial screening of titles and abstracts for eligibility (Figure 1). A large majority of records did not meet our inclusion criteria because they reviewed studies of steroid-induced osteoporosis, surgical postmenopausal osteoporosis, secondary osteoporosis, or other women patient groups with co-morbidities (e.g. breast cancer, transplant patients, kidney disease, diabetes). Another common reason for papers to be excluded from analysis was they were not reviews. Of the 211 potentially eligible records, another 19 studies did not meet our inclusion criteria and a further 18 articles could not be retrieved for full-text assessment because authors did not reply to our requests (n=12) or the review had been withdrawn (n=6); hence, they were excluded from further evaluation.

We retrieved 174 full-text papers for full assessment, of which a further 47 did not meet our inclusion criteria, primarily because they reported pooled results rather than subgroup analyses of postmenopausal women separately. In particular, we found that our search for reviews of treatment for osteoporotic fractures (vertebroplasty and balloon kyphoplasty) yielded 14 potentially eligible citations but 12 of these did not disaggregate the reviewed results for postmenopausal women; there was a tendency in this literature to consider results for older people of both sexes together, with subgroup analyses reported for different settings of care provision (e.g. community-dwelling, nursing home residents, hospital).

A total of 128 eligible studies were included for data extraction and quality review. Of these, seven studies were rated as of very high quality and 22 of high quality. A further 17 studies were considered of medium quality while the remainder was of below medium quality (n=82). Figure 2.1 outlines our search strategy results.

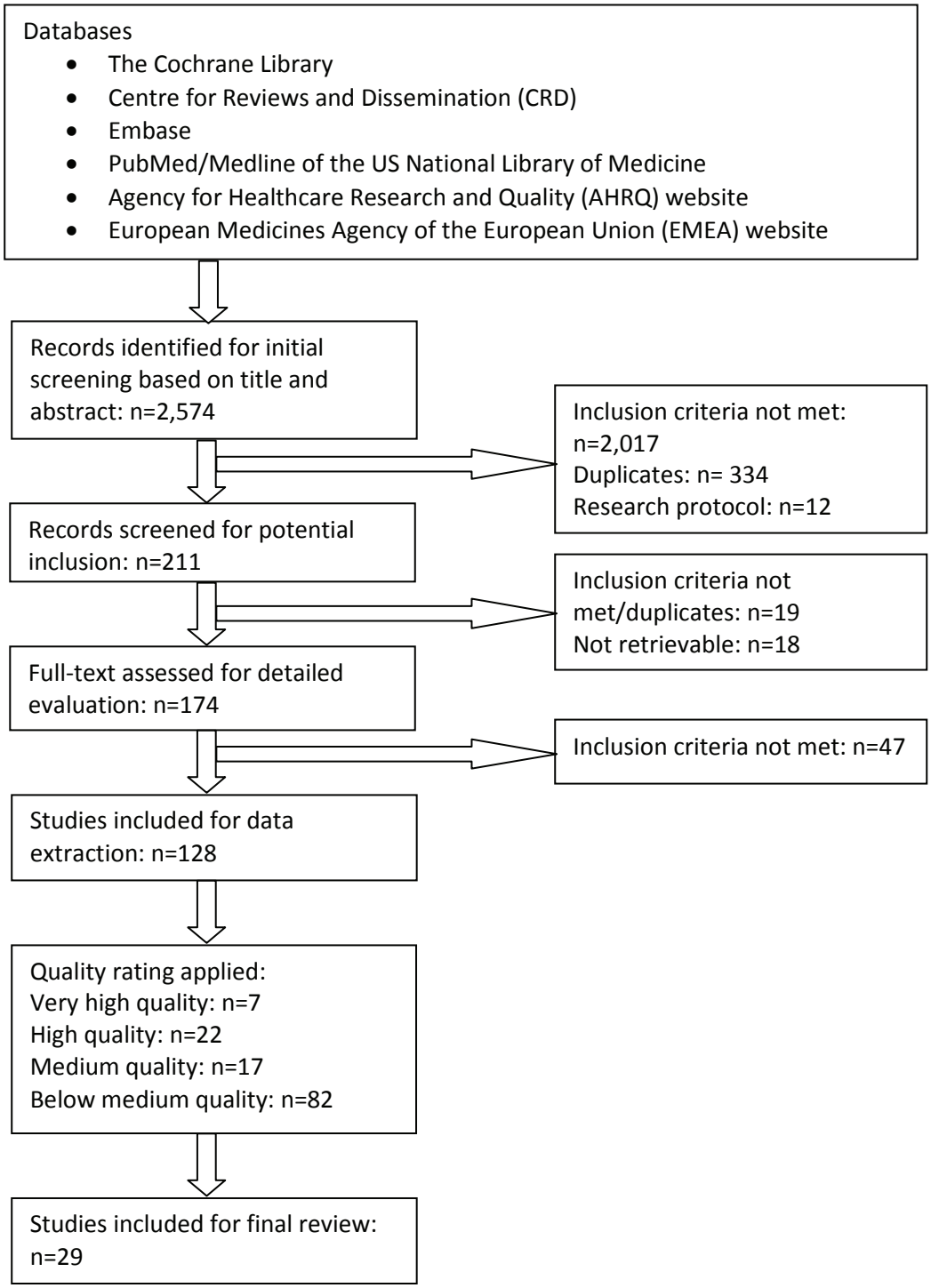

Figure 2.1 Search strategy

In what follows, we report on the 29 studies identified as high or very high quality reviews and meta-analyses. Of these, four examined diagnostic approaches to the assessment of fracture risk; twelve examined pharmacological interventions, of which three evaluated the

cost-effectiveness or cost-utility of a given pharmacological intervention; seven examined non-pharmacological interventions; and seven combined different interventions (pharmacological agents, or non-drug and drug therapies), of which one also reviewed osteoporosis screening.

Comparing studies judged as of medium quality or lower with those rated as of high or very high quality, we did not identify systematic differences related to publication year, sources searched, interventions assessed, or review method (narrative vs meta-analysis). Rather, studies judged as of medium quality or lower did not meet specific criteria considered mandatory. For example, such studies failed to make explicit inclusion and/or exclusion criteria, they did not report on the search strategy (e.g. databases used, dates searched, language limits) and/or how studies were screened for eligibility for inclusion, or whether studies included were assessed for quality. Typically, reviews and meta-analyses considered of below medium quality did not provide clear definitions of terms such as efficacy and/or effectiveness or did not explicitly discuss study limitations. However, we did not consider these criteria as mandatory.

2.2.1 Identifying risk factors and assessing screening tools

We identified one review of factors associated with low BMD,[11] which found that evidence supported the selection of women aged 40–60 years with low body weight for BMD assessment. We also identified two reviews and a meta-analysis examining the efficacy or effectiveness of screening tools for risk assessment.[12-14] Although no effectiveness trials could be identified concerning population-wide screening, there is an evidence base on the performance of fracture risk assessment and bone measurement instruments: two reviews suggested that using simple assessment tools or few clinical risk factors were equally useful to more complex instruments, but another found uncertain performance of a simple tool to rule out low BMD.

Waugh et al. (2009) reviewed the evidence from 13 observational studies on risk factors associated with low BMD in healthy women between the ages of 40 to 60 years.[11] Of a total of 13 potential risk factors, the authors reported good evidence for low body weight and postmenopausal status to increase the risk for low BMD, while the evidence did not support an association with BMD of moderate alcohol consumption, caffeine intake or reproductive history. Moreover, the evidence was inconsistent or insufficient regarding an association between BMD and other risk factors: calcium intake, physical activity, smoking, age at menarche, history of amenorrhea, family history of osteoporosis, race and current age. Based on their review, the authors concluded that only healthy women aged 40–60 years with low body weight (<70kg) be selected for BMD assessment; they identified a need for further research on populations other than Caucasian women and for evaluating the risk factors for which the evidence was inconclusive.

Nelson et al. (2010) failed to identify any trials on the effectiveness and harms of population-wide osteoporosis screening in reducing fractures, morbidity and mortality.[13] However, their review of 40 observational studies on the performance of risk assessment and bone measurement instruments found that clinical risk factors modestly predicted low bone density (area under the curve (AUC) value, 0.13–0.87; 14 instruments in 23 studies) and fractures (AUC, 0.48–0.89; 11 instruments in 10 studies). Instruments considering fewer clinical risk factors, such as age and BMD only, were found to perform similarly to

those considering a wider range of factors, for example the FRAX fracture risk assessment tool. The review did not identify studies that provided evidence for risk-assessment tools to improve fracture outcomes. Among bone density measurement techniques, calcaneal quantitative ultrasonography was found to predict fracture outcomes but correlated poorly with bone density assessment at the femoral neck using DXA, which predicted hip fracture best. The authors highlighted a lack of data on the frequency with which BMD measurement should be undertaken, with findings from one longitudinal study pointing to lack of effect on predictive performance for fracture outcomes after repeat measurement within an eight year interval. Overall, the review by Nelson and colleagues (2010) suggested considerable uncertainty remained about the effectiveness of population-wide screening for osteoporosis, its harms and, if implemented, screening intervals, with further clarity required on the identification of subgroups for whom screening is most effective.[13]

Also focusing on risk factor screening tools, McLeod and Johnson (2009), in a review of twenty observational studies, identified six risk factor screening tools as providing an effective means for identifying postmenopausal Caucasian women at increased risk of low BMD and developing osteoporosis who would benefit from subsequent assessment using DXA measurement (Table 2.2).[12] These were: Simple Calculated Osteoporosis Risk Estimation (SCORE); the Osteoporosis Risk Assessment Instrument (ORAI); the Osteoporosis Self-Assessment Tool (OST); the body weight criterion (pBW); the Osteoporosis Index of Risk (OSIRIS); and Age, Body Size, No Estrogen (ABONE). The OST instrument was identified as a particularly appropriate screening tool for use in daily practice with acceptable discriminatory capacity. Conversely, a meta-analysis of 31 observational studies of the performance of OST to rule out low BMD in postmenopausal women found its clinical usefulness to remain uncertain.[14] It is worth noting that only three of the studies analysed by Rud et al. (2007)[14] were also included in the review by McLeod and Johnson (2009)[12] and that the studies included in Rud et al. (2007)[14] were assessed by the authors as being of low methodological quality, calling into question the representativeness and generalisability of findings on the OST.

Table 2.2 Summary of screening tools reported by McLeod and Johnson (2009)

Screening tool	Sensitivity range (median)	Specificity range (median)	AUC range (median)
ABONE	0.56–0.83 (0.70)	0.48–0.84 (0.66)	0.72–0.72 (0.72)
BW	0.72–0.94 (0.9)	0.35–0.53 (0.42)	0.13–0.79 (0.68)
ORAI	0.5–1.00 (0.92)	0.00–0.75 (0.45)	0.32–0.8 (0.76)
OSIRIS	0.64–0.85 (0.79)	0.39–0.69 (0.51)	0.71–0.73 (0.72)
OST	0.78–0.95 (0.88)	0.37–0.71 (0.5)	0.33–0.82 (0.76)
SCORE	0.80–1.00 (0.96)	0.07–0.63 (0.23)	0.59–0.85 (0.74)

NOTES: ABONE, Age, Body Size, No Estrogenrogen; BW, body weight criterion; ORAI, Osteoporosis Risk Assessment Instrument; OSIRIS, Osteoporosis Index of Risk; OST, Osteoporosis Self-Assessment Tool; SCORE, Simple Calculated Osteoporosis Risk Estimation; AUC, area under the curve

SOURCE: McLeod and Johnson (2009)[12]

2.2.2 Treatment of osteoporosis and prevention of fracture: pharmacological interventions

We identified 12 reviews and meta-analyses of pharmacological interventions, examining bisphosphonates (n=4), denosumab (1), calcitonin (1), calcium and vitamin D (3),

selective oestrogen receptor modulators (1) and strontium ranelate (2). Although our search also identified analyses and reviews of raloxifene, parathyroid hormone peptides, HRT and fluoride, none of these met our assessment of high or very high quality. If a high or very high quality review covered more than one of these categories of intervention in their reporting, they are discussed in Section 2.2.4, 'Combinations of pharmacological agents and of drug and non-drug interventions', below.

Several reviews also reported on study findings related to adverse events or side-effects.[13 15-24] For example, Anastasilakis et al. (2009) identified a statistically significant difference among randomised controlled trials (RCTs) reviewed for serious side-effects and/or death.[15] Others pointed to a potential risk for gastrointestinal injury (alendronate, etidrondate, risderonate and strontium ranelate);[19 22-24] osteonecrosis of the jaw (alendronate and risedronate);[22 24] vascular and nervous system side-effects (strontium ranelate, raloxifene, oestrogen);[13 19 21] and leg cramps (teriparatide) and back pain (alendronate).[17]

Bisphosphonates

Four meta-analyses examined bisphosphonates, including three Cochrane reviews. Some papers discussed bisphosphonates among other types of intervention, which are discussed later in this paper. Alendronate and risedronate were identified as reducing risk of all fracture types among postmenopausal women with low BMD or prior fracture; but etidronate only reduced vertebral fractures when these factors were present. Alendronate was the only bisphosphonate to show fracture risk reduction even among postmenopausal women without low BMD or prior fracture.

Wells et al. (2008a) examined the efficacy of alendronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women, drawing on 11 RCTs.[22] The meta-analysis identified alendronate (equivalent of a daily dose of 10mg) to be effective in reducing vertebral, non-vertebral, hip and wrist fracture risk among those with evidence of low BMD or prior fracture, with risk reductions of around 50 percent for vertebral, hip and wrist fracture and about 25 percent for non-vertebral fractures (Table 2.3). For those with little or no evidence of low BMD or without prior fracture, risk reductions were also observed but these were statistically significant for vertebral fractures only: relative risk (RR): 0.53; 95% confidence interval (CI), 0.37, 0.76.

In a separate review, Wells et al. (2008b) assessed the efficacy of etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.[23] Based on a meta-analysis of 11 other RCTs, they demonstrated, for a dosage of 400mg per day, a significant reduction in fracture risk of about 50 percent for women with low bone mineral density or prior fracture. There was no significant risk reduction for fractures other than vertebral (non-vertebral, hip, wrist) in this population or among women with little or no evidence of low BMD or without prior fracture (Table 2.3).

Two meta-analyses assessed risedronate. Cranney et al. (2002) reviewed the effect of risedronate on bone density and fractures in postmenopausal women, drawing on eight RCTs.[25] Their analyses provided evidence for risedronate substantially reducing the risk of both vertebral and non-vertebral fractures of 27 percent and 36 percent respectively (daily dose of 2.5mg or more) (Table 2.3). This was accompanied by an increase in bone density of the lumbar spine and femoral neck in both early postmenopausal women and those with

established osteoporosis. The analysis also demonstrated that the increase in bone density was greater at higher daily dosages of 5mg, with for example the percentage change in bone density after the final year of treatment (1.5 to 3 years) equating to 4.54 percent (95% CI 4.12, 4.97) for the lumbar spine.

In a more recent study that aimed to assess the efficacy of risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women, Wells et al. (2008c)[24] analysed seven RCTs which, apart from one, had also been reviewed by Cranney et al. (2002).[25] Their meta-analysis demonstrated that 5mg dosages of risedronate significantly reduced the risk of vertebral, non-vertebral and hip fractures among women with low BMD or prior fracture, with risk reductions ranging from 20 percent for non-vertebral fractures to 40 percent for vertebral fractures (Table 2.3). There was no statistically significant effect of risedronate on fracture risk for women with little or no evidence of low BMD or without prior fracture.

Denosumab

We identified little high quality evidence on denosumab that did not appear to support its role in reducing fracture risk against the safety evidence at the time of the review.

Anastasilakis et al. (2009) reviewed nine RCTs to determine the efficacy and safety of denosumab in postmenopausal women with osteoporosis.[15] The authors drew on three RCTs for their meta-analysis; however one of these involved patients having nonmetastatic breast cancer. The two which focused on the target population of our analysis had contrasting results in fracture risk reduction: one found effects favouring denosumab (OR: 0.27; 95% CI 0.05, 1.31), whereas the other found effects favouring controls (OR: 3.23; 95% CI 0.42, 24.57). Both found serious adverse events and infection risk for women assigned to denosumab compared to controls (fixed effects). The review had identified an unpublished large, international RCT called Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM); this could potentially change the evidence reviewed, which suggested strong safety issues of the therapy of little efficacy.

Selective oestrogen receptor modulators

Our search did not identify high or very high quality reviews addressing treatment with selected oestrogen receptor modulators (SERMs) such as raloxifene; however, a recent meta-analysis of ten RCTs evaluated the effectiveness of soy isoflavone supplementation on BMD in women as a potential alternative to hormone therapy since isoflavones act as selective oestrogen receptor modulators.[26]

Liu et al. (2009) found a weak beneficial effect of soy isoflavones on lumbar spine BMD only with a large dose (≥80mg/day) of soy isoflavones (weighted mean difference, WMD=6.0mg/cm^2/year, 95% CI 0.7, 12.7).[26] The authors concluded that soy isoflavone supplementation was unlikely to have a significant favourable effect on BMD at the lumbar spine and hip in women.

Calcitonin

The effects of calcitonin were examined in a meta-analysis of five RCTs by Knopp et al. (2005) for the treatment of acute pain in patients with osteoporotic fractures.[27] The analyses showed that calcitonin significantly reduced the severity of pain in patients sustaining stable, recent osteoporotic vertebral compression fractures, with pain at rest

being reduced as early as one week into treatment (WMD: 3.08, 95% CI 2.64, 3.52) and continuing weekly to four weeks (WMD: 4.03, 95% CI 3.70, 4.35). A similar reduction in pain was shown for sitting, standing and walking, while gastrointestinal side-effects were minor and tended to be self-limited. The authors concluded that calcitonin appeared effective in the management of acute pain associated with acute osteoporotic vertebral compression fractures as it shortened the time to mobilisation.

Calcium and vitamin D

Three meta-analyses assessed the efficacy or effectiveness and safety of vitamin D and calcium supplementation in postmenopausal women to prevent osteoporosis or related fractures.[18 20 28] The evidence showed that vitamin D reduced new vertebral fractures and, when combined with calcium supplementation, also reduced non-vertebral fractures (hip); the combined therapy even showed some effect on reducing falls in postmenopausal women.

Drawing on 25 RCTs, Papadimitropoulos et al. (2002) found that treatment with vitamin D significantly reduced the incidence of vertebral fractures (RR: 0.63, 95% CI 0.45, 0.88) but incidence of non-vertebral fractures had a non-significant reduction (RR: 0.77, 95% CI 0.57, 1.04).[20] Trials using hydroxylated vitamin D consistently demonstrated a larger impact on bone density than standard vitamin D although the authors were not able to assess comparative effectiveness of standard and hydroxylated vitamin D because of lack of sufficiently detailed data at the time of review. Papadimitropoulos et al. (2002) noted that vitamin D treatment appeared to increase the risk of discontinuing medication (RR: 1.37, 95% CI 1.01, 1.88) because of symptomatic adverse effects or abnormal laboratory results.[20]

More recently, Cranney et al. (2007) aimed to assess the effectiveness of supplemental doses of vitamin D on BMD and fracture or fall risk, using a meta-analysis of 106 RCTs.[18] While the overall evidence of whether vitamin D supplementation reduces fractures and its effects on falls was found to be inconsistent, there was some evidence that vitamin D reduced fractures in institutional settings (OR: 0.69, 95% CI 0.53, 0.90) and of a small overall benefit on falls in postmenopausal women (OR: 0.80, 95% CI 0.66, 0.98), in particular for combinations of vitamin D3 with calcium supplementation (OR: 0.84, 95% CI 0.76, 0.93). Intakes of vitamin D above current reference amounts did not increase the risk of adverse events. The authors concluded that specific subgroups received a small benefit on BMD and reduced risk of fractures and falls compared with placebo when treated with vitamin D3 at a dose of at least 700 IU/day supplemented with calcium.

The combined effect of supplementation was further examined in a recent meta-analysis of nine RCTs, with a focus on the need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation.[28] The analysis found a non-significant increase in hip fracture risk for vitamin D alone (RR: 1.10, 95% CI 0.89, 1.36), while the combination of vitamin D and calcium supplementation significantly reduced the risk of hip fracture by 18% compared with no treatment (RR: 0.82, 95% CI 0.71, 0.94). The authors further demonstrated that combining vitamin D with additional calcium reduced the risk of hip fracture by 25% compared to supplementation with vitamin D only (adjusted RR: 0.75, 95% CI 0.58, 0.96). Based on their findings, Boonen et al. (2007) concluded that clinical efficacy of oral vitamin D (700–800 IU/day) would be optimised

when complemented with calcium (daily dose 1,000–1,200mg) while pointing to the need for further research to identify those individuals who will benefit most from combined therapy.[28]

Strontium ranelate

We identified two evidence synthesis reports examining strontium ranelate, both showing a significant reduction in vertebral and non-vertebral fractures.[19 21]

O'Donnell et al. (2006) aimed to determine the efficacy and safety of strontium ranelate for the treatment and prevention of postmenopausal osteoporosis, based on four RCTs.[19] The analysis found strontium ranelate (equivalent of daily dose of 2g over three years) to be effective in reducing vertebral fractures by 37% (RR: 0.63, 95% CI 0.56, 0.71) and non-vertebral fractures by 14% (RR: 0.86, 95% CI 0.75, 0.98). Strontium ranelate was further found to be effective in increasing BMD after two to three years of treatment in lumbar spine adjusted for strontium content (WMD: 2.14, 95% CI 0.70, 3.58; 2.1g/day), femoral neck (WMD: 2.52, 95% CI 0.96, 4.09; 2.1g/day) and total hip (WMD: 9.83, 95% CI 9.27, 10.39; 1.2g/day). A clear dose-response was observed for fracture reduction and BMD increase. The increase in femoral neck BMD, for example, was 2.52 (95% CI 0.96, 4.09) with 2.1g/day and 8.25 (95CI 7.84, 8.66) with 4.2g/day. Treatment was not discontinued because there were adverse events, although vascular and nervous system side-effects did increase with 2g of daily strontium ranelate intake over three to four years. In brief, the authors concluded that vertebral fractures and to some extent non-vertebral fractures were reduced with strontium ranelate.

Stevenson et al. (2007) examined the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fracture in postmenopausal women, using three RCTs.[21] The analysis found strontium ranelate to be associated with a significant reduction in the risk of vertebral fracture and non-vertebral fracture of respectively 40 percent and 16 percent (Table 2.3). While generally there was no association with increased risk of adverse events which tended to be mild and transient, strontium ranelate significantly increased the risk for venous thromboembolism (RR: 1.42; 95% CI 1.02, 1.98). Based on these findings, the authors concluded that strontium ranelate is clinically effective in the prevention of osteoporotic fractures although highlighting the need for further research into the effectiveness in relation to hip fractures. The findings of the cost-effectiveness analysis of strontium ranelate undertaken by the authors will be reported below.

2.2.3 Non-pharmacological interventions

We identified six meta-analyses and one review of non-pharmacological interventions. These included resistance training;[29] targeted or impact exercise;[30-31] walking;[32] Tai Chi;[33] whole-body vibration;[34] and a range of interventions aimed at enhancing the quality of services delivered in the community.[35] Resistance training, particularly when there is a mix of high and low impact, appeared effective at preserving and increasing BMD at the lumbar spine among postmenopausal women; but this effect was not found for walking or Tai Chi. Hip BMD appeared to increase with whole-body vibration. A range of one-to-one patient counselling interventions also showed improvements in outcomes such as quality of life and lifestyle modifications. However, most reviews noted the limitations of

existing evidence in this area as RCTs tended to be short and few in number with poorly defined outcome measures.

Kelley et al. (2001) analysed 29 studies (18 RCTs) on the impact of resistance training on bone mineral density in pre- and postmenopausal women.[29] They found that resistance training preserved lumbar spine BMD and increased lumbar spine BMD for postmenopausal women at the proximal femur (0.33% increase in exercise group vs 0.05% decrease in control), lumbar spine (0.19% increase in exercise group vs 1.45% decrease in control) and radius (1.22% increase in exercise group vs 0.95% decrease in control). In a more recent meta-analysis of 15 trials (10 RCTs), Martyn-St James and Carroll (2009) examined different exercise protocols on postmenopausal bone loss.[30] They showed that a combination of high and low impact exercises, and high and low resistance exercises, were more effective at preserving and increasing BMD than one particular type of exercise on its own, particularly for hip and spine BMD.

Nikander et al. (2010) performed a meta-analysis of four RCTs and ten meta-analyses, examining long term (>6 months) effects of supervised exercise.[31] The analysis found some evidence that resistance training may increase lumbar spine BMD by 1–2% but not femoral neck BMD. Endurance training or walking appeared to have little or no effect on BMD at either site. Overall, it was concluded that current evidence was still limited by the small number and short average duration of the available RCTs of exercise effects on bone strength.

Two recent meta-analyses assessed the efficacy or effectiveness of less intensive forms of physical activity, such as walking or Tai Chi. Drawing on eight studies, Martyn-St James and Carroll (2008) concluded that regular walking had no significant effect on the preservation of BMD at the spine in postmenopausal women, except at the femoral neck, which identified statistically significant increases (Table 2.3).[32] However, the effect of walking was considered too small to be of clinical significance to account for fracture prevention. Similarly, reviewing three RCTs and one controlled clinical trial examining Tai Chi on BMD change in postmenopausal women, Lee et al. (2008) did not identify a statistically significant effect, as compared with no treatment (at the spine), resistance training (for total hip), or exercises or calcium supplementation generally.[33] However, studies were considered as of poor methodological quality and the available evidence considered as not sufficient to support the notion that Tai Chi may be effective in the prevention or treatment of osteoporosis.

Slatkovska et al. (2010) examined the impact on BMD of whole-body vibration.[34] Based on an intention-to-treat analysis of five RCTs in postmenopausal women, whole-body vibration significantly increased hip areal BMD (WMD: 0.015g/cm^2, 95% CI 0.008, 0.022) compared with controls, but not spine areal BMD (WMD: −0.003g/cm^2, 95% CI −0.012, 0.005) or tibia trabecular volumetric BMD (WMD: −2.2mg/cm^3, 95% CI −10.0, 5.7). As the whole-body vibration regimes varied in the studies reviewed, which tended to be of short duration, the authors identified a need for larger scale, long-term studies to better understand the effects of this intervention and to enable identifying the applicability of this technology in clinical practice.

Lai et al. (2010) assessed 24 RCTs for the effects of a range of non-pharmacological interventions that aimed at enhancing the quality of services provided to postmenopausal

women with osteoporosis.[35] Interventions included patient education, home-based assessment of fall and fracture risk, feedback on test results, helping to detect and treat osteoporosis, supervised exercise and/or physiotherapy. Outcome measures were quality of life, BMD, medication adherence and lifestyle modification. The review found evidence for improvements in quality of life for patient education (leaflet plus review, or a 50-minute consultation over five weeks), supervised physical therapy and/or exercise, and home-based simple exercise with follow-up calls. Interventions that were positively associated with adherence to medication included: nurse monitoring with or without feedback on bone marker turnover, and patient education on the need to continue treatment with feedback on bone marker turnover. Nutrition education, feedback on health status using DXA scan results with or without patient education as well as one-to-one counselling with follow up and high frequency of exercise were found to be associated with improved calcium intake. Overall, Lai et al. (2010) showed that patient-centred consultations can have important effects on a range of outcomes, although the authors caution that some outcome measures remain ill-defined and require further refinement.

2.2.4 Combinations of pharmacological agents and of drug and non-drug interventions

We identified seven studies that examined a range of interventions of various pharmacological and non-pharmacological types, either as single interventions or in combination, including six meta-analyses[3 13 16 36-38] and one review.[17]

Kanis (2002) aimed to assess the effectiveness of pharmacological and non-pharmacological interventions in preventing osteoporotic fractures in patients with osteopaenia, osteoporosis or established osteoporosis, based on an analysis of 83 RCTs.[37] Interventions included: bisphosphonates, vitamin D (and hydroxylated derivatives), calcitonin, calcium, oestrogens and oestrogen-like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, vitamin K2, protein supplements and exercise. Using fractures as the primary outcome measure of treatment of established osteoporosis, the study found bisphosphonates, calcitonin, calcium, fluoride salts and raloxifene to be effective in reducing the incidence of vertebral fracture, with alendronate also shown to reduce the risk of non-vertebral fracture, including of the hip (Table 2.3). Furthermore, it showed calcium to be effective in patients with low calcium intakes, and when calcium is taken in combination with vitamin D. There was no evidence from studies considered in the review that vitamin D derivatives, oestrogen, oestrogen-like molecules, anabolic steroids, protein supplements or brisk walking reduced the risk of fracture. For treatment with bisphosphonates, fluoride and SERMS, there was no significant difference in the risk of fracture when patients were stratified according to the presence or absence of prevalent vertebral fractures. The authors found that a lack of appropriate RCTs meant that many agents failed to demonstrate efficacy for hip fracture.

Stevenson et al. (2005) performed a review of 90 RCTs to assess the clinical effectiveness and cost-effectiveness of a range of interventions for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in postmenopausal women.[38] For vertebral fracture, they found alendronate, etidronate, risedronate, raloxifene and teriparatide all to reduce risk in women with severe osteoporosis and considered to have adequate dietary calcium intakes (see Table 2.3 for a range of relative risk reductions) or vitamin D intakes (alendronate, raloxifene). For non-vertebral fracture, only risedronate and teriparatide were associated with a significant risk reduction. Calcium, alone or in

combination with vitamin D, was also shown to reduce fracture risk. None of these interventions was identified to be significantly more effective than either of the other active interventions examined.

Brandão et al. (2008) reviewed 32 RCTs of pharmacological interventions for the treatment of osteoporosis, considering bisphosphonates, HRT, parathyroid hormone and other interventions.[17] The primary outcomes of interest were vertebral fractures or lumbar spine BMD. Alendronate was shown to reduce vertebral fractures in two out of five studies with evidence of an association with an increase in lumbar spine BMD compared with placebo or raloxifene. Risedronate was found to be associated with an increase in lumbar spine BMD compared with placebos, although differences did not appear significant. Ibandronate reduced vertebral fractures and increased BMD compared with placebos, but the magnitude of the effect seems to depend on dose and administration route (oral or intravenous). Intravenous ibandronate at 2mg every three months appeared to have the best efficacy compared with placebo and to oral treatment. Evidence for raloxifene appeared inconsistent, with some evidence based on a single study demonstrating a significant increase in lumbar spine BMD but also an increase in the risk of vertebral fracture at higher doses (120mg). Strontium ranelate was found to be effective in increasing lumbar spine BMD and reducing vertebral fracture incidence but the effects appeared to be dose-dependent. Finally, Brandão et al. (2008) included one study of hormone replacement therapy (HRT), which showed statistically significant reductions in new vertebral fractures when oestrogen and progesterone were combined and in increased lumbar spine BMD when in combination with alendronate; however, the authors discussed the controversy of HRT's association with increased risk of coronary disease and breast cancer, among others.

Avenell et al. (2009) examined 45 trials to determine the anti-fracture effect of vitamin D.[16] They found that vitamin D alone appears unlikely to be effective in preventing hip fracture, vertebral fracture or any new fracture. However, when vitamin D is taken with calcium, it reduces hip fractures (RR: 0.84, 95% CI 0.73, 0.96). Overall, hypercalcaemia is significantly more common in people receiving vitamin D or an analogue, with or without calcium; this is especially true of calcitriol. There is a modest increase in gastrointestinal symptoms and a small but significant increase in renal disease. The authors concluded that vitamin D with calcium may result in fewer hip fractures, but vitamin D alone is unlikely to prevent fracture.

Nelson et al. (2010) sought to assess pharmacological interventions for the primary prevention of osteoporosis and low bone density, reviewing 29 RCTs.[13] Bisphosphonates, parathyroid hormone, raloxifene and oestrogen were shown to reduce primary vertebral fractures and bisphosphonates also reduced primary non-vertebral fractures. They further found that bisphosphonates were associated with a significantly decreased risk of vertebral fracture compared with placebos, with relative risks of between 0.55 and 0.63 (Table 2.3). Smaller but significant effects on non-vertebral and hip fracture were also observed with alendronate and risedronate, but not etidronate. Evidence of harm associated with pharmacological treatments was found for raloxifene (thromboembolic events) and oestrogen (thromboembolic events, stroke, and coronary heart disease and breast cancer when in combination with progestin).

MacClean et al. (2007) assessed the effectiveness and safety of treatments to prevent fractures in osteoporotic persons and treatment adherence, reviewing 149 RCTs, 62 meta-analyses and 53 observational studies.[3] They found that alendronate, risedronate, denosumab and zoledronic acid reduced the risk of vertebral, non-vertebral and hip fractures. Ibandronate and PTH (teriparatide) reduced the risk of vertebral fractures and non-vertebral fractures, but not necessarily hip fractures. Raloxifene reduced the risk of vertebral fractures, even in low risk postmenopausal women. Wrist fractures were reduced by alendronate. Moreover, when alendronate was combined with calcium, the risk of any type of clinical fracture was significantly decreased as compared with alendronate alone. However, the effect of calcium alone on fracture risk appeared unclear from several large high quality RCTs, which showed low compliance of the therapy overall and only compliant postmenopausal women appeared to have reduced fractures with calcium treatment. Moreover, the effect of vitamin D on fracture risk was uncertain because of the mixed results in the existing evidence.

Making head-to-head comparisons of different treatments, MacClean et al. (2007) identified few RCTs comparing drugs within a given class (e.g. bisphosphonates) and the data reviewed did not appear to demonstrate that any one agent was superior in preventing fractures.[3] Drugs from different classes were also rarely compared and available information did not appear to demonstrate that bisphosphonates were better at preventing fractures than calcium, PTH, or raloxifene or hormone therapy. Finally, the review found no RCT data comparing the exercise against any of the pharmacological agents reviewed.

Bolland et al. (2010) examined mortality as an outcome of various pharmacological treatments, showing that risedronate, strontium ranelate, zoledronic acid or denosumab were associated with a small but significant reduction in mortality of old frail individuals who have osteoporosis.[36]

Table 2.3 Summary of results from included reviews

						Participants			*Person-years*		
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**	
Wells al. (2008a)[22]	Alendronate	10mg	Vertebral	Primary		**0.55**	0.38	0.8	**0.53**	0.37	0.76
		10mg	Vertebral	secondary		**0.55**	0.43	0.69	**0.49**	0.29	0.82
		10mg	non-vertebral	Primary		0.89	0.76	1.04	0.91	0.77	1.07
		10mg	non-vertebral	secondary		**0.77**	0.64	0.92	**0.74**	0.61	0.89
		10mg	Hip	Primary		0.79	0.44	1.44	0.79	0.43	1.45
		10mg	Hip	secondary		**0.47**	0.26	0.85	**0.47**	0.26	0.85
		10mg	Wrist	Primary		1.19	0.87	1.62	1.19	0.87	1.63
		10mg	Wrist	secondary		**0.5**	0.34	1.73	**0.5**	0.34	0.73
Wells et al. (2008b)[23]	Etidronate	NR	Vertebral	Primary		3.03	0.32	28.44	3	0.32	28.5
			Vertebral	secondary		**0.53**	0.32	0.87	**0.45**	0.31	0.64
			non-vertebral	Primary		0.56	0.2	1.61	0.56	0.19	1.63
			non-vertebral	secondary		1.07	0.72	1.6	1.04	0.68	1.58
			Hip	Primary		-			-		
			Hip	secondary		1.2	0.37	3.88	1.14	0.34	3.9
			Wrist	Primary		-			-		
			Wrist	secondary		0.87	0.32	2.36	0.8	0.27	2.37
Cranney et al. (2002)[25]	Risedronate	All	Vertebral	primary and secondary pooled		**0.64**	0.54	0.77			

						Participants			*Person-years*		
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**	
		All	non-vertebral	primary and secondary pooled		**0.73**	0.61	0.87			
Wells et al. (2008c)[24]	Risedronate	5mg	vertebral	primary		0.97	0.42	2.25	0.94	0.4	2.21
		5mg	vertebral	secondary		**0.61**	0.5	0.76	**0.59**	0.47	0.73
		5mg	non-vertebral	primary		**0.81**	0.25	2.58	**0.78**	0.24	2.53
		5mg	non-vertebral	secondary		**0.8**	0.72	0.9	**0.49**	0.28	0.87
		5mg	hip	primary		-			-		
		5mg	hip	secondary		**0.74**	0.59	0.94	**0.74**	0.58	0.93
		5mg	wrist	primary		-			-		
		5mg	wrist	secondary		0.67	0.42	1.07	0.65	0.41	1.04
Anastasilakis et al. (2009)[15]	Denosumab	various	any	primary and secondary		ODDS .74	0.33	1.64			
Liu et al. (2009)[26]	Soy isoflavones	87mg (mean over 1 year)	BMD change lumbar spine		random effects model	WMD 4.1	−1.6	9.8			
			BMD change femoral neck		fixed effects model	WMD −1.5	−7.2	4.3			
			BMD change total hip		random effects model	WMD 2.5	−0.5	5.4			
Knopp et al. (2005)[27]	Calcitonin	1 week into treatment	pain in vertebral fractures	secondary	fixed effects model	WMD 3.08	2.64	3.52			

						Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
		4 weeks into treatment		secondary	fixed effects model	WMD 4.03	3.7	4.35		
Papadimitropoulos et al. (2002)[20]	Vitamin D	standard	vertebral			0.33	0.01	8.05		
			all non-vertebral			0.78	0.55	1.09		
		hydroxylated	vertebral			**0.64**	0.44	0.92		
			all non-vertebral			0.87	0.29	2.59		
		combined	vertebral			0.63	0.45	0.88		
			all non-vertebral			0.77	0.57	1.04		
Boonen et al. (2007)[28]	Vitamin D	varied	hip			1.1	0.89	1.36		
	Vitamin D with calcium	varied	hip			**0.79**	0.64	0.97		
Cranney et al. (2007)[18]	Vitamin D2 or D3 with or without calcium vs placebo or calcium	varied	all fractures			ODDS 0.9	0.81	1.02		
	Vitamin D3 with calcium vs placebo	varied	all fractures			ODDS 0.87	0.76	1		
	Vitamin D3 with or without calcium vs placebo	varied	hip			ODDS 0.83	0.68	1		

						Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
O'Donnell et al. (2006)[19]	Strontium ranelate	0.5–2g per day over 3 years	vertebral	secondary		0.63	0.56	0.71		
		0.5–2g per day over 3 years	non-vertebral	secondary		0.86	0.75	0.98		
Stevenson et al. (2007)[21]	Strontium ranelate		vertebral			**0.6**	0.53	0.69		
			non-vertebral			**0.84**	0.73	0.97		
Kanis et al. (2002)[37]	Alendronate		vertebral			0.536	0.439	0.656		
			non-vertebral			0.825	0.736	0.926		
	Etidronate		vertebral			0.434	0.236	0.8		
			non-vertebral			1.011	0.681	1.501		
	Risedronate		vertebral			0.628	0.506	0.779		
			non-vertebral			0.737	0.559	0.972		
	bisphosphonates		vertebral	primary		0.558	0.387	0.805		
				secondary		0.575	0.49	0.675		
	bisphosphonates		non-vertebral	primary		0.889	0.761	1.039		
				secondary		0.813	0.693	0.954		
	Vitamin D derivatives		vertebral			1.03	0.62	1.71		
			non-vertebral			1.353	0.348	5.257		

Study	Intervention	Dose	Fracture location	Women with fracture (secondary) or without fracture (primary)	Method	*Participants* Relative risk	95% confidence interval		*Person-years* Risk reduction	95% confidence interval
	Vitamin D derivatives against calcitriol control		vertebral			1.152	0.688	1.928		
			non-vertebral			2.03	0.457	9.025		
	Vitamin D derivatives against alfacalcidol control		vertebral			0.459	0.0149	1.414		
			non-vertebral			0.193	0.007	5.068		
	Fluoride		vertebral	primary		0.25	0.078	0.797		
				secondary		0.686	0.544	0.864		
			non-vertebral	primary		0.412	0.13	1.308		
				secondary		0.998	0.788	1.268		
	SERMs		vertebral	primary		0.575	0.436	0.757		
				secondary		0.674	0.581	0.78		
			non-vertebral	primary		-	-	-		
				secondary		-	-	-		
Stevenson et al. (2005)[38]	Alendronate		vertebral	primary		0.34	0.04	3.25		
				secondary		0.53	0.41	0.68		
			non-vertebral	primary		0.88	0.47	1.64		
				secondary		0.81	0.65	1.01		

							Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**			**Risk reduction**	**95% confidence interval**
			hip	primary		-	-	-			
				secondary		0.49	0.24	1.01			
	Etidronate		vertebral	primary		-	-	-			
				secondary		0.43	0.2	0.91			
			non-vertebral	primary		-	-	-			
				secondary		1.04	0.64	1.69			
			hip	primary		-	-	-			
				secondary		0.5	0.05	5.34			
	Risedronate		vertebral	primary		-	-	-			
				secondary		0.63	0.51	0.78			
			non-vertebral	primary		0.14	0.01	2.6			
				secondary		0.67	0.5	0.9			
			hip	primary		-	-	-			
				secondary		0.6	0.42	0.88			
	Raloxifene		vertebral	primary		-	-	-			
				secondary		0.69	0.56	0.86			
			non-vertebral	primary		-	-	-			
				secondary		-	-	-			
			hip	primary		-	-	-			
				secondary		-	-	-			
	Teriparatide		vertebral	primary		-	-	-			

Study	Intervention	Dose	Fracture location	Women with fracture (secondary) or without fracture (primary)	Method	Participants: Relative risk	Participants: 95% confidence interval		Person-years: Risk reduction	Person-years: 95% confidence interval
				secondary		0.35	0.22	0.55		
			non-vertebral	primary		-	-	-		
				secondary		0.65	0.43	0.98		
			hip	primary		-	-	-		
				secondary		0.5	0.09	2.73		
	Calcium		vertebral	primary		1.26	0.65	2.46		
				secondary		0.55	0.33	0.93		
			non-vertebral	primary		-	-	-		
				secondary		-	-	-		
			hip	primary		-	-	-		
				secondary		-	-	-		
	Calcium with vitamin D		vertebral	primary		2.95	0.21	71.21		
				secondary		-	-	-		
			non-vertebral	primary		0.79	0.69	0.92		
				secondary		-	-	-		
			hip	primary		0.72	0.59	0.88		
				secondary		-	-	-		
	Calcitriol		vertebral	primary		4.44	0.5	39.03		
				secondary		1.02	0.44	2.32		
			non-vertebral	primary		0.46	0.17	1.27		

						Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
				secondary		2.5	0.51	12.19		
			hip	primary		-	-	-		
				secondary		-	-	-		
	HRT		vertebral	primary		2.05	0.71	5.97		
				secondary		0.58	0.26	1.3		
			non-vertebral	primary		0.86	0.72	1.02		
				secondary		0.67	0.12	3.93		
			hip	primary		0.67	0.32	1.43		
				secondary		-	-	-		
Brandão et al. (2008)[17]	No figures given, no meta analysis									
Avenell et al. (2009)[16]	Vitamin D		hip			1.15	0.99	1.33		
			vertebral			0.9	0.42	1.92		
			any			1.01	0.93	1.09		
	Vitamin D with calcium		hip			0.84	0.73	0.96		
Nelson et al. (2010)[13]	Alendronate		vertebral	primary		0.6	0.44	0.83		
			non-vertebral	primary		0.88	0.55	1.4		
			hip	primary		0.78	0.44	1.38		
			wrist	primary		0.76	0.27	2.16		

Study	Intervention	Dose	Fracture location	Women with fracture (secondary) or without fracture (primary)	Method	Participants: Relative risk	Participants: 95% confidence interval		Person-years: Risk reduction	Person-years: 95% confidence interval
			ankle	primary		0.4	0.08	2.07		
	Combined bisphosphonate		vertebral	primary		0.66	0.5	0.89		
			non-vertebral	primary		0.83	0.64	1.08		
			hip	primary		0.7	0.44	1.11		
			wrist	primary		0.67	0.25	1.82		
			ankle	primary		0.33	0.08	1.44		
	Parathyroid hormone		vertebral	primary		0.32	0.14	0.75		
			non-vertebral	primary		0.97	0.71	1.33		
			hip	primary		-	-	-		
			wrist	primary		-	-	-		
			ankle	primary		-	-	-		
	Raloxifene		vertebral	primary		0.61	0.54	0.69		
			non-vertebral	primary		0.97	0.87	1.09		
			hip	primary		0.97	0.62	1.52		
			wrist	primary		0.83	0.66	1.05		
			ankle	primary		0.94	0.6	1.47		
	Oestrogen with progestin		vertebral	primary		0.66	0.46	0.92		
			non-vertebral	primary		-	-	-		
			hip	primary		0.67	0.47	0.96		

							Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**			**Risk reduction**	**95% confidence interval**
			wrist	primary		0.71	0.69	0.85			
			ankle	primary		0.71	0.69	0.85			
	Oestrogen only		vertebral	primary		0.62	0.42	0.93			
			non-vertebral	primary		-	-	-			
			hip	primary		0.61	0.41	0.91			
			wrist	primary		-	-	-			
			ankle	primary		-	-	-			
Bolland et al. (2010)[36]	Risendronate, strontium ranelate, zoledronic acid, denosumab	various	mortality	secondary		0.89	0.8	0.99			
Kelley et al. (2001)[29]	Resistance training	16 weeks (minimum)	BMD femur	primary and secondary	Effect size and boot-strapped confidence intervals	0.07+−0.36	−0.02	0.15			
			BMD lumbar spine	primary and secondary	Effect size and boot-strapped confidence intervals	0.24+−0.36	0.11	0.38			

							Participants		*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
			BMD radius	primary and secondary	Effect size and boot-strapped confidence intervals	0.3+−0.33	0.13	0.48		
Martyn-St James and Carroll (2009)[30]	Impact exercise	median 12 months	BMD lumbar spine		random effects model	WMD 0.015	0.005	0.025		
					fixed effects model	WMD 0.014	0.01	0.018		
			BMD femoral neck		random effects model	WMD 0.008	0.004	0.013		
					fixed effects model	WMD 0.005	0.003	0.007		
			BMD hip		random effects model	WMD 0.013	0.001	0.024		
					fixed effects model	WMD 0.02	0.017	0.023		
Nikander et al. (2010)[31]	Targeted exercise	varied	BMD distal tibia		Standard mean difference (SMD), random effects	SMD 0.08	−0.21	0.37		

						Participants			*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
			BMD tibial midshaft		Standard mean difference, random effects	SMD −0.07	−0.3	0.16		
			BMD proximal tibia		Standard mean difference, random effects	SMD 0.14	−0.63	0.92		
			BMD femoral midshaft		Standard mean difference, random effects	SMD −0.01	−0.77	0.75		
			BMD femoral neck		Standard mean difference, random effects	SMD 0.02	−0.27	0.3		
			BMD overall		Standard mean difference, random effects	SMD 0	−0.15	0.15		
Martyn-St James and Carroll (2008)[32]	Walking	6–24 months	BMD lumbar spine		fixed effects model	WMD 0.006	−0.004	0.001 6		
			BMD femoral neck		fixed effects model	WMD 0.012	−0.001	0.026		

							Participants		*Person-years*	
Study	**Intervention**	**Dose**	**Fracture location**	**Women with fracture (secondary) or without fracture (primary)**	**Method**	**Relative risk**	**95% confidence interval**		**Risk reduction**	**95% confidence interval**
Lee et al. (2008)[33]	Tai Chi	32–280 sessions for 40–60 minutes	BMD lumbar spine		random effects model	WMD 0.02	−0.02	0.06		
Slatkovska et al. (2010)[34]	Whole-body vibration		BMD hip			WMD 0.015	0.008	0.022		

NOTES: Significance level reported in bold. Abbrev: BMD, bone mineral density; NR, not reported; SERMs, selective oestrogen receptor modulators; ODDS, odds ratio; WMD, weighted mean difference

2.3 Discussion

This review of reviews identified 128 reviews which met our inclusion criteria. However, less than a quarter of these were assessed as of high or very high quality (n=29). These were generally meta-analyses reporting on either a given pharmacologic agent (a bisphosphonate, denosumab, calcitonin, calcium and vitamin D, selective oestrogen receptor modulators and strontium ranelate) or non-pharmacological interventions (resistance training, targeted or impact exercise, walking, Tai Chi, whole-body vibration and patient-centred interventions); or on a combination of agents and/or intervention types, which were often compared 'head-to-head'. Moreover, most of the reviews and analyses we identified reported on BMD, even though the predictive value of BMD for fracture risk is known to be low.[3 39-40]

Before discussing our findings, some limitations of the analysis as presented here must be considered. First, as a review of reviews we did not examine the original studies and we can therefore not determine the potential bias introduced in the reporting by the authors. It is also possible that some studies which we graded as of medium quality or lower were incorrectly classified because they did not report on a particular quality criterion because of restrictions on space, for example. At the same time, given the large body of literature in this field, it may be argued that reviews and meta-analyses ought to provide sufficient methodological detail to enable readers to judge quality. A further limitation might relate to the language limitations imposed by our review, which meant that we had to exclude a few potentially eligible citations because they were written in languages other than English. However, given the proportion of high quality reviews from the total included, it is unlikely that our analysis will have been affected by those that could not be assessed for inclusion. Finally, a clear limitation of a review of reviews is that it fails to consider more recent original studies not yet included in reviews but which may be relevant and important, as for example emerging evidence examining a possible association between bisphosphonate use and atypical fractures.[41-42]

A key observation from our review of reviews is that that there is a comparatively large and diverse body of literature on interventions to prevent, diagnose and/or treat osteoporosis in postmenopausal women. Differential impacts of interventions by population subgroups, fracture location and dosing regimes might explain the limited number of studies which compare head-to-head different pharmacological agents with and between drug classes and the lack of trials comparing non-drug interventions, such as exercise, against pharmacological treatment, such as bisphosphonates. This reflects, to large part, the complexity of the underlying condition that the interventions that are being assessed are aiming to address.

We find that the majority of the reviews analysed here appear to draw on the same body of primary evidence rather than corroborating evidence from multiple different studies or trials. This in turn reflects a scarcity of high quality or comparable evidence in those areas. While it is clear that some areas of research are in need of further advancement, with greater cross-agent comparisons, there may also be a need to (re-)define priorities for further research. For example, much of the evidence presented here relies on findings of randomised controlled trials, viewed as the gold standard of proof for intervention-effect

relationships.[43] However, the usefulness of the randomised controlled design in the field of complex conditions such as osteoporosis or, more broadly, fracture risk may be questioned. The challenges are inherent in the nature of trials that focus on a specific intervention in a highly selected population, often excluding those whose characteristics, in particular their age, would have excluded them from the trials that demonstrated their effectiveness.[44] Thus, the disparities between results reported in trials of postmenopausal women and those obtained in routine clinical practice may mean that much of the reputed evidence base for clinical decisions is, to some degree, of limited value.[45]

The current evidence base provides an abundance of detailed information on many of the available therapeutic modalities for postmenopausal osteoporosis. However, there are some areas that remain poorly understood, indicating the need for further large-scale, long-term research. For example there is a need to better understand how exercise, or other non-pharmacological therapies, compares head-to-head with pharmacological agents; or to investigate the effectiveness of population-based screening, including screening intervals, the identification of subgroups for whom screening is most effective, or indeed any harms that may be associated with population-based screening. Furthermore, although there is good evidence on the effects of selected treatments on clinical outcomes, there remains considerable need to better understand the optimal use (frequency, quantity, duration) of pharmacological interventions for preventive purposes; the combinations of pharmacological and/or non-pharmacological interventions that may prevent any type of fracture (not specific to a particular site); and specific populations who would benefit from a given intervention or who have not been studied, as in the case of combined therapy of vitamin D with calcium in non-Caucasian women.

At the same time, the evidence that is available can inform quality improvement in clinical practice. For example, available evidence suggests that simple risk factor assessment tools can provide effective means to identify postmenopausal women who would benefit from further diagnostic assessment, such as DXA scanning. Yet, as we will see in Chapter 3, this knowledge is not widely implemented, with available evidence pointing to considerable levels of under-diagnosis and under-treatment of osteoporosis and associated fractures, even where relevant guidelines for clinical practice have been instituted.[40] Future research may therefore more usefully focus on identifying barriers to for example guideline implementation.

Finally, it is worth noting that our review of the available literature identified a larger number of reviews that were excluded rather than included because effect sizes for men and women were pooled and/or subgroup analyses were not reported for treatments such as vertebroplasty. While this observation may reflect, in part, reporting of findings in the studies concerned, it is likely that there is also an assumption that pooled effect sizes are unproblematic for developing the evidence on treatment of osteoporotic fractures in aged populations which are predominantly female. Future work might usefully examine whether it is indeed the case in clinical practice that osteoporotic fracture treatments have similar effects on women and men, given that the efficacy of different pharmacological agents for fracture prevention in the very elderly remains an area for further research.[38] There is also a need for more clarity on treatment efficacy versus effectiveness. A majority of reviews included in our review did not provide an explicit definition of either term or else they did not provide sufficient detail about the setting of trials reviewed to enable the reader to

differentiate between the two concepts. Thus, high quality reviews reported on treatment effectiveness by drawing on data from randomised controlled designs, which are unlikely to adequately capture effects found in real-world settings.

Part II. Managing postmenopausal osteoporosis in Europe: Experiences in four countries

CHAPTER 3 Managing postmenopausal osteoporosis in Europe

In this chapter, we review current practices to managing postmenopausal osteoporosis in Europe by means of case studies of four countries: England, France, Germany and Spain. We focus on four areas: (a) national strategies to managing osteoporosis in postmenopausal women; (b) guidelines in place and evidence of their use; (c) uptake of preventive and therapeutic interventions; and (d) the quality of care for those with osteoporosis and osteoporosis-related fractures. We begin by outlining our analytical approach and then describe key findings, which are organised as country-specific sections. We conclude with a section drawing together the key emerging observations from country experiences.

3.1 Methods

3.1.1 Evidence review

We performed a review of the published and grey literature as identified from the standard bibliographic database PubMed. In order to capture the potentially varied literature we applied broad search terms, using combinations of ('/' indicating 'or'): 'prevent$/manage$/therapy/organisation/treat$ [Title/Abstract]' combined with 'osteoporosis[Title/Abstract]' and '[Name of country]'. Countries considered were England/UK, France, Germany and Spain (see below). The search was limited to studies published from 2000 onwards. We imposed this restriction mainly because of the considerable developments in the diagnosis and pharmacological treatment of osteoporosis during the 2000s. Studies predating these developments are unlikely to inform a better understanding of contemporary approaches to the management of osteoporosis in healthcare. We considered studies published in English, French, German and Spanish language.

Titles and abstracts were screened for eligibility for inclusion. Studies considered eligible were retrieved where possible and scrutinised further for inclusion or exclusion in the review. References cited in studies considered eligible were followed up where appropriate. We generally excluded studies that commented on or reviewed the management of osteoporosis generally, randomised trials and intervention studies that tested a new treatment or intervention, and aetiological studies. We also excluded studies that examined the cost-effectiveness of a given intervention and of adherence and/or persistence to osteoporosis medication.

This search was complemented by targeted searches of information provided by governmental and non-governmental agencies and organisations involved in the organisation and financing of care and/or the development of guidelines in the countries under review (see below), as well as national and international organisations including the International Osteoporosis Foundation (IOF).

As part of the evidence review, we also extracted the national guidelines for the management of osteoporosis and osteoporosis-related fractures. Relevant guidelines were identified from national and international organisations as listed above. We analysed the guidelines by means of a structured template, extracting information on a range of features including guideline scope, goal and target group; risk assessment; principal diagnostic examination; bone density measurement; criteria for pharmaceutical treatment; recommended drugs; and monitoring and duration of treatment. An overview of the main features of the guidelines in place in the four countries under review is presented in Appendix A.

3.1.2 Key informant interviews

The review of the literature described above was complemented by interviews with key informants with documented expertise in the field of osteoporosis prevention and/or treatment identified from the relevant scientific literature. Informants were invited to participate in a 45 minute telephone interview. They were provided, in advance, with a structured questionnaire addressing our four areas of interest: (a) national strategies to managing osteoporosis in postmenopausal women; (b) guidelines in place and evidence of their use; (c) uptake of preventive and therapeutic interventions; and (d) the quality of care for those with osteoporosis and osteoporosis-related fractures. We further invited key informants to provide a list of up to five indicators they considered suitable for the monitoring and assessment of the management of osteoporosis or osteoporosis-related fractures among postmenopausal women. Informants were given the choice to provide written responses where telephone interview was not possible or desired. An abbreviated version of the interview topic guide is provided in Appendix B.

For each country considered for review (see below), we identified three to four key informants, selected because of their track record in the scientific literature as identified from the literature search described in the preceding chapter and/or their role as advisors in national or international organisations. Each potential participant was invited by email outlining the purpose of the study and their role as an interviewee. Despite repeated reminders, and, in a third round of reminders, adding a small fee, only three key informants agreed to participate, representing France, Germany and England (written response). We were unable to secure an interview partner for Spain. This very low response rate may be explained, in part, by the period of data collection, which coincided with the summer holiday period in several countries although we did allow for a rather wide timeframe, from early July to end of September 2011. More importantly, we approached leading experts in the field who were unable to respond to our request mainly because of multiple competing commitments. This poses a challenge to our analysis in so far as the identification of potential quality indicators for the management of postmenopausal osteoporosis in this report has had to rely on a single response in three out of four countries only. The proposed list of quality indicators will therefore have to be interpreted

with caution, and any guidance derived from these data will have to be considered as preliminary and in need of further confirmatory work.

3.1.3 Country selection

Countries reviewed were selected on the basis of (a) the main approach to funding (taxation, statutory health insurance, combination) and organisation of healthcare services; and (b) level of usage of medicines for the treatment of osteoporosis as identified in a recent report by Ström et al. (2011).[40] Based on these considerations, we selected four countries: England/UK, France, Germany and Spain.

Table 3.1 provides an overview of selected characteristics of the healthcare system in each of the countries. The countries provide a fairly broad range of approaches to healthcare organisation and governance. Thus, in France and Germany, funding is based, largely, on statutory health insurance whereas both England and Spain operate a tax-based, national health service. The four systems involve different degrees of (de-)centralisation of decision-making, of national-level guideline development and whether or not GPs act as a gatekeeper to specialist care. In all countries, office-based doctors outside hospital tend to be self-employed, but the usual method of payment differs. Those in France and Germany are traditionally paid on a fee-for-service basis while GP practices in England and Spain usually receive capitation as the basic form of payment.

It should be noted that we principally focus on England rather than the United Kingdom, given the diverging changes following the devolution of responsibility for the NHS to governments in England, in Northern Ireland, Scotland and Wales from 1999.[46] However, where evidence retrieved applies to the UK as a whole, as for example in the context of national guidelines or in international comparative studies such as that by Ström et al. (2011)[40], we refer to the UK.

Table 3.1 Overview of key characteristics of healthcare in four countries

	England (UK)	France	Germany	Spain
Health expenditure (2009)				
Percent GDP	9.8 (UK)	11.8	11.6	9.5
Per capita expenditure (US$ PPP)	3,487 (UK)	3,78	4,218	3,067
Main sources of funding for healthcare (percent of total health expenditure, 2009)				
Taxation	84.1	5.5	8.7	69.1
Social security contributions	-	72.5	68.2	4.6
Out-of-pocket payments	10.5	7.3	13.1	20.1
Voluntary health insurance	1.1	13.3	9.3	5.4
Principles of healthcare provision				
Provision of primary/generalist care	Primary care teams including GPs, nurses and other health professionals	Office-based primary and specialist care physicians	Office-based primary and specialist care physicians	GPs in health centres

	England (UK)	France	Germany	Spain
Choice of provider in primary/ ambulatory care	Within defined geographical area of residence	Yes	Yes	Varies across regions; typically limited to limited to GPs available in the users' region
Provision of specialist care	Specialist care physicians principally based in hospital	Specialist care physicians based outside (office-based) and in hospitals	Specialist care physicians based outside (office-based) and in hospitals	Specialist care physicians mainly based in hospital
GP gatekeeping	Yes	Voluntary ('preferred doctor')	Voluntary ('GP contracts')	Yes; direct access certain specialists, eg gynaecologists, paediatricians
Payment of physicians in primary/ambulatory care	Basic payment of GPs through nationally negotiated contract (GMS contract); combination of capitation, fee-for-service and performance-related pay (QOF)	Fee-for-service; nationally set fee based on agreements between professional organisations and statutory health insurance administration; performance-related element (CAPI) from 2009 based on individual contracts between GP and statutory health insurance	Combination of capitation and fee-for service based on centrally negotiated 'uniform value scale' (EBM) by the Federal Association of statutory health insurance physicians and the National Association of statutory health insurance Funds	Combination of salary and age-weighted capitation payment
Provision of hospital care	Government owned hospitals ('hospital trusts')	Public (including private non-for-profit) and private for-profit hospitals	Public, private-for profit and private non-profit	Public and private hospitals (40 percent of private hospital income funded by public system)
Principal mechanism for payment for hospital care	Activity-related payment using healthcare resource groups (HRGs)	Activity-based funding system using diagnosis-related groups (DRGs)	Activity-based funding system using diagnosis-related groups (DRGs)	Varies by region
Payment of health professionals working in hospital	Salary	Salary (public hospitals)	Salary	Salary

SOURCES: Ettelt et al. (2006)[47]; Chevreul et al. (2010)[48]; Ettelt and Nolte (2010)[49];Garcia-Armesto et al. (2010)[50]; Nolte et al. (2011)[51]; OECD (2011)[52]

In what follows we provide country-specific sections, each giving (a) a brief overview of main features of the country's healthcare system; (b) a summary overview of the documented evidence of the burden of disease associated with osteoporosis and/or fracture; (c) strategies and guidelines in place; (d) principles of financing and management of postmenopausal osteoporosis and (e) an overview of the evidence on the quality of care provided for postmenopausal osteoporosis.

3.2 England

3.2.1 The healthcare system

Healthcare in England is primarily organised and delivered through the National Health Service (NHS). It is funded through general taxation, including a small national insurance contribution, accounting for about 84.1 percent of total health expenditure in 2009.[52] The NHS covers all residents, and health services are free at the point of use, with few exceptions such as prescription drugs and dental care[53]; out-of-pocket payments account for 10.5 percent (2009) of total health expenditure and voluntary health insurance for another 1 percent. In 2009, national health expenditure in the UK overall was 9.8 percent of gross domestic product.[52]

The NHS is overseen by the Department of Health (DH), with ten strategic health authorities (SHAs) providing oversight at regional level. A number of bodies at arm's length from the Department of Health, such as the National Institute for Health and Clinical Excellence (NICE) and the Care Quality Commission, have assumed a range of key regulatory and quality assurance functions, including monitoring provider performance, issuing national guidelines and developing national standards.

Approximately 80 percent of the NHS budget is currently devolved to 151 primary care trusts (PCTs), which are responsible for organising the delivery of care for geographically defined populations through a mix of direct service provision and commissioning of primary, secondary and community care. Under current government plans, this function will be fully devolved to consortia of GP-led clinical commissioning groups, with PCTs and SHAs set to be disbanded in 2014. Oversight will be delegated to a newly created NHS Commissioning Board.[54]

Most primary care healthcare services in England are provided by primary care teams, including general practitioners (GPs), nurses and other health professionals, usually in community-based GP practices or health centres. GPs act as gatekeepers to secondary and specialist care services provided by salaried doctors and nurses in public hospitals (NHS trusts and foundation trusts). Some publicly financed care is also provided by private and voluntary providers. Most GPs operate privately under a national contract, with their income paid by primary care trusts. Services provided by NHS trusts and foundation trusts, are increasingly paid on the basis of activity, which, in 2006/07, accounted for about 60 percent of acute trust income.[55]

3.2.2 Country burden attributed to postmenopausal osteoporosis and associated fractures

In 2010, the population in the United Kingdom was about 61.3 million, with the proportion of those aged 65 years and older at 16 percent (80 years and over: 4.2 percent).[52]

Analyses of general practice data in England and Wales for the late 1990s estimated the lifetime risk of any fracture among women aged 50 years at 53.2 percent (men: 20.7 percent).[56] More recently, Wu et al. (2011), using hospital discharge data, showed how age-standardised hip fracture rates in England have remained fairly stable over a ten-year period between 1998 and 2009, at around 102 per 100,000 person years.[57] Rates among women were about three times those in men (women: 156.6 and 153.5/100,000; men:

44.6 and 51.8/100,000), and highest among those aged 85 years and older. The absolute number of hip fractures increased, reflecting the changing demographic profile especially among the oldest population segments.

Burge et al. (2001) projected, based on the natural history of osteoporosis, for the number of fractures associated with osteoporosis in the UK population aged 50 years and older, to rise from 190,000 in 2000 to 230,000 per annum in 2020.[58] Other estimates predicted an increase in the annual rate of hip fractures from 46,000 in 1989 to 117,000 in 2016.[59] The annual direct costs attributed to osteoporosis-related fractures were estimated to increase by 20 percent, from £1.8 billion in 2000 to over £2.1 billion in 2020.[58] Cumulative totals for the period 2000–2010 were estimated at 2.2 million fractures and £20.3 billion.

At the same time, while the overall number of fractures attributable to osteoporosis is projected to increase, available evidence points to a decline in associated mortality. Thus, Wu et al. (2011) demonstrated how in-hospital mortality following fracture fell by 16.5 percent between 1998 and 2008, from 126.9 to 106.0 deaths per 1000 hip fracture admissions, pointing to improvements in surgical and medical treatment of hip fracture patients.[57] The greatest absolute decline was among those aged 85 years and over while those living in deprived areas had a higher risk of in-hospital death following admission for hip fracture.

3.2.3 Strategies and guidelines for osteoporosis

The prevention and treatment of osteoporosis is part of an agenda to promote health throughout life, as set out in the 2001 National Service Framework (NSF) for Older People in England.[60] The standards include strategies to reduce the number of falls, fractures and serious injuries and emphasise preventing chronic illness such as osteoporosis.

Specific guidelines were issued in 1999 by the Royal College of Physicians (RCP) for the treatment and prevention of postmenopausal osteoporosis to identify patients at high fracture risk[61-62], followed by 2002 guidance on the prevention and treatment of glucocorticoid-induced osteoporosis.[63]

In 2002, the National Institute of Health and Clinical Excellence (NICE) commenced an appraisal process for the development of guidance on osteoporosis, with guidance on the secondary prevention of fracture first issued in 2005.[39] This was subsequently expanded to also address primary prevention and include one additional therapy (strontium ranelate), published in 2007.[64] However, the guidance was subject to a succession of appeal, amendment, judicial review, further amendment and appraisal and further appeal, and following further judicial review in 2010, NICE was tasked to issue new guidance.[39] The latter re-appraisal was in relation to strontrium ranelate and in January 2011, NICE concluded that, having examined additional evidence submitted by the manufacturer, and in agreement with a newly set up appraisal committee, to retain the recommendation as published in 2008 and reissued in 2010.[65-67] While the latest appeal and judicial review concerned strontium ranelate in particular, other concerns centred around the appraisal process and assumptions on the economic model used by NICE.[68]

Also in 2010, NICE issued guidance on the use of denosumab, recommending it as a possible treatment for preventing bone fractures in some postmenopausal women with osteoporosis who are unable to take bisphosphonates.[69] NICE is also in the process of

developing a short clinical guideline on *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk,* work on which had been placed on hold following the discussions around the technology appraisals on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women described above.[70]

In parallel, and in recognition of new developments in particular with regard to the better understanding of clinical risk factors that contribute to fracture risk, the National Osteoporosis Guideline Group (NOGG) was established in 2008 by professional societies across the UK, including the Royal College of Physicians, the Bone Research Society, the British Geriatric Society, the British Orthopaedic Association, the British Society of Rheumatology, the Society of Endocrinology and others to develop a clinical guideline for the management of persons at high fracture risk.[71-72] Principally building on the earlier guidance issued by the Royal College of Physicians, the NOGG guideline is aimed at providing thresholds for the use of fracture probabilities at which a BMD assessment might be recommended, incorporating the FRAX® risk assessment tool developed by the WHO to calculate an individual's 10-year probability of fracture based on clinical risk factors, with or without femoral neck BMD.[73]

There is limited empirical evidence that has compared the performance of NICE guidance and the NOGG guidelines. For example, Clark et al. (2010) reported that NICE guidelines for the secondary prevention of osteoporotic fragility fractures in post-menopausal women might lead to over-treatment of this age group.[74] NICE guidance recommends the treatment with bisphosphonates of patients older than 75 years if DXA measurement is clinically inappropriate. However, when analysing DXA scans in a group of patients over the age of 75 years with sustained fragility fracture, Clark et al. (2010) identified these as not osteoporotic.[74] Byrne et al. (2010) examined how recommendations for treatment compare when using guidance from NOGG and guidance from NICE, finding disagreement in 28 percent of cases, with younger patients being more likely to qualify for treatment according to NOGG.[75] However, neither study has as yet been published as full paper so findings are difficult to interpret.

It is important to note that clinical guidelines developed by NICE apply to England and Wales only; NOGG guidelines have been developed by organisations across the United Kingdom.

3.2.4 Financing and managing postmenopausal osteoporosis

In the NHS, access to DXA assessment and treatment of postmenopausal osteoporosis is largely determined by healthcare practitioners following NICE guidance. Access is free of charge where criteria set out by the guidance are met. Individuals with osteoporosis or those at high risk of fracture are identified opportunistically using a case-finding strategy developed by the Royal College of Physicians; there is currently no universally accepted policy for population-based screening. Specialties involved in the treatment of osteoporosis include general practice, rheumatology, orthopaedics, endocrinology, metabolic medicine, geriatrics, and obstetrics and gynaecology. Patients presenting to hospital with a fracture are usually seen first, and often solely, by an orthopaedic surgeon.[76-77]

Pro-active case finding in primary care requires coordination between primary and secondary care to enable identification of patients with or at risk of osteoporosis who are

expected to benefit from the national service framework for older people.[78] In 2006/07, the national General Medical Services (GMS) contract which stipulates the basic payment of GPs, was amended to reward general practices for providing 'enhanced services' and so support national priorities for patient services. These 'directed enhanced services' (DES) are voluntary but must be provided in collaboration with the PCT; they include the diagnosis and prevention of osteoporosis (Osteoporosis Diagnosis and Prevention Scheme).[79] Providers contracted under this scheme must have established and maintain a register of all female registered patients aged 65 and older with fragility fractures (Fragility Fracture Register) and payment is calculated on the basis of the proportion of women patients on the register who meet a set of defined conditions:

(i) aged 65 to under 75 years, have sustained a fragility fracture and have been referred for a DXA scan during the financial year;

(ii) aged 65 to under 75 years, have sustained a fragility fracture, have had a diagnosis of osteoporosis confirmed by DXA scan and receive treatment with a bone-sparing agent; or

(iii) aged 75 years or over, have sustained a fragility fracture and are receiving treatment with a bone-sparing agent.

For example, in financial year 2008/09, a contractor who had 50 percent or more women patients on the register meeting criterion (i) would have received a maximum payment of £197.07; no payment would be made if the proportion was 20 percent or less. In 2010/11, the payment schedule was amended, requiring a minimum of 60 percent of patients meeting criterion (i), with the payment equating to £199.48 while the threshold for non-payment was increased to 40 percent or less.

More recently, steps have been taken to include osteoporosis indicators into the Quality and Outcomes Framework (QOF). The QOF is a voluntary pay-for-performance scheme that was implemented with the 2004 national GMS contract and that linked up to 25 percent of GP practice income to performance.[80] Following local piloting of indicators, the Independent Primary Care Quality and Outcomes Framework Indicator Advisory Committee recommended, in June 2011, for three indictors on osteoporosis/fragility fractures to be included on the NICE menu for consideration for QOF.[81] This is used by the General Practitioners Committee of the British Medical Association and NHS Employers in their contract negotiations. The three indicators are[82]:

(i) The practice can produce a register of patients:
    1. aged 50–74 years with a record of a fragility fracture after 1 April 2012 and a diagnosis of osteoporosis confirmed on DXA scan, and
    2. aged 75 years and over with a record of a fragility fracture after 1 April 2012

(ii) The percentage of patients aged between 50 and 74 years, with a fragility fracture, in whom osteoporosis is confirmed on DXA scan, who are currently treated with an appropriate bone-sparing agent.

(iii) The percentage of patients aged 75 years and over with a fragility fracture, who are currently treated with an appropriate bone-sparing agent.

This implies that funding for the prevention and treatment of postmenopausal osteoporosis may eventually be obtained through the Quality Outcomes Framework of the GP contract.

3.2.5 Evidence on quality of care for postmenopausal osteoporosis

Using international sales data on prescription drugs as a proxy for treatment, Ström et al. (2011) estimated that, in the UK in 2008, 5.7 percent of the population aged 50 years did take up the treatment for osteoporosis.[40] They further estimated that there were about 11.5 million women aged 50 years or older in the UK, of whom approximately 8.9 percent were being treated (these numbers are based on the assumption that women receive 87 percent of all prescribed treatment). Relating these figures more specifically to those with osteoporosis as defined by bone mineral density, an estimated 40 percent of women aged 50 years and older with osteoporosis were treated for the condition. This proportion is slightly higher if related to those who exceed the fracture risk threshold for treatment. This identifies a 'treatment gap' of 56 percent, implying that less than half of those eligible for treatment do indeed receive it.

Empirical work on the quality of care in relation to the prevention and treatment of postmenopausal osteoporosis in England (and the UK more widely) is comparatively patchy, frequently relying on selected settings (e.g. one hospital) although three more recent national-level assessments provide important insights, pointing to suboptimal levels of the prevention and treatment of osteoporosis in England.

One study of a large district general hospital in the south west of England found that only 3 percent of patients undergoing surgery for fracture of the femoral neck were discharged on treatment for osteoporosis and no further treatment was started despite osteoporotic re-fractures among 23 percent of patients.[83] The analysis did not provide any detail on age of patients. Talbot et al. (2007) reviewed pre- and post-fracture medication of 175 patients older than 55 years who had sustained a distal radial fracture during a 20-month period in 2003 and 2004, in one teaching hospital in England.[84] They found that just a third of patients had been prescribed fracture prevention treatment including calcium and vitamin D (22 percent) and bisphosphonates (9 percent). Only 8.5 percent had been referred for bone density measurement. Less than half of the patients who had commenced inpatient treatment had continued on medication in primary care. The 2010 national audit of falls and bone health in older people reported somewhat higher although still substandard intervention levels, with only 33 percent of those with non-hip fracture and 60 percent of hip fracture patients receiving appropriate management for bone health.[85]

These findings might be reflective of a level of uncertainty as to the responsibilities for managing osteoporosis and related fractures in the system. A survey of UK geriatricians carried out in the early 2000s found relatively high awareness levels with 83 percent reporting that they carried out falls assessment in their patients and 95 percent initiated treatment (bisphosphonates and/or calcium or vitamin D) for osteoporosis directly.[86] At the same time, while most specialists had access to BMD measurements, one third did not use it. Based on a multinational survey of osteoporotic fracture management by orthopaedic surgeons, Dreinhöfer et al. (2005) found that in the UK the majority of those surgeons would refer a patient with suspected osteoporosis on to an osteoporosis specialist or GP, while only about 20 percent would directly initiate BMD measurement for such a patient.[77] Just under 40 percent of surgeons would prescribe bisphosphonates for those

with osteoporosis and just under 60 percent would prescribe calcium and vitamin D (approximately 50 percent). Importantly, while the majority of respondents believed that they should identify and initiate the assessment of osteoporosis in patients with fragility fractures, only about 25 percent reported feeling knowledgeable about managing the condition. Furthermore, only 16 percent of orthopaedic surgeons noted that they should take the responsibility for treatment, believing this to be the responsibility of family-practice doctors, rheumatologists and endocrinologists.

Care gaps between primary and secondary care could potentially be bridged by means of improved communication and coordination, through for example a fracture liaison nurse. Comparing two groups of fracture patients at two orthopaedic centres in the UK (Scotland), Murray et al. (2005) reported that implementing a fracture liaison service (FLS) in one centre had resulted in 85 percent of patients with proximal humeral fracture and 20 percent with hip fracture being offered a DXA scan.[87] These figures were, respectively, 6 percent and 9.7 percent in the second centre, which had relied on individual clinicians. The authors further noted that 50 percent (proximal humeral) and 85 percent (hip) fracture patients in the FLS centre received treatment for osteoporosis, compared with respectively 27 percent and 20 percent in the second centre. Similarly, Charalambous et al. (2009) reported that having an osteoporosis and fracture liaison specialist nurse present in an orthopaedic fracture clinic increased the referral catchment rate to 77 percent compared with only 1.6 percent when referrals relied on doctors, or 63 percent when patients were asked to self-refer.[76] However, the 2010 national audit of falls and bone health in older people reported that only 37 percent of local health services provided any form of fracture liaison service, and if they did, this did not necessarily ensure reliable assessment of all fracture patients.[85]

Evidence on the quality of care provided to those at risk residing in care homes remains patchy. Aspray and colleagues (2006) assessed predictors of fracture risk and treatment for osteoporosis among older care home residents in the north of England, finding a high prevalence of osteoporosis, at between two-thirds and 75 percent, while prescription rates for bisphosphonates were very low, at between 1 percent and 2 percent, as was calcium and vitamin D supplementation (between 3 percent and 12 percent).[88] The underuse of calcium and vitamin D among house-bound or institutionalised older people was also documented in an earlier study by Kayan et al. (2003); reporting on a postal survey of geriatricians across the UK, they found that only 16 percent of older patients admitted to hospital from an institutional care home had received supplementation.[86] A more recent assessment of osteoporosis management in primary care reported somewhat higher treatment levels among populations in residential or nursing care homes, with 37 percent of those aged 75 years and older receiving current treatment with a combined calcium and vitamin D preparation.[89] Aspray et al. (2006) emphasised the need for targeted education of medical and nursing professionals in care homes,[88] although training for care homes, for example on when to refer to primary care or how to identify falls risk, remains low.[85]

While still suboptimal, higher treatment rates can be observed for the primary care setting overall. For example, drawing on the 2004–2005 wave of the English longitudinal study of ageing, Steel et al. (2008) found the self-reported receipt of care for osteoporosis as indicated by guidance on high quality care among people aged 50 years and more to range between 49 percent and 57 percent.[90] More recently, the 2007 'Evaluation of standards for

osteoporosis and falls in primary care' commissioned by the NHS Information Centre found that 59 percent of patients with evidence of osteoporosis received specific osteoporosis treatment.[89] This proportion was higher for older women (65–74 years) with a history of fragility fracture and diagnosed osteoporosis, at just under 75 percent. At the same time, only one in ten older women with a previous fragility fracture had had a referral for bone density assessment in her electronic medical record. Furthermore, older women with a prior fragility fracture were found to be less likely to receive guideline care than those at younger ages. The study was based on an analysis of electronic medical records, noting that the recording system was in need of improvement. For example, the analysis found that about half of the prescriptions for osteoporosis treatment were for patients without a documented diagnosis of this condition. This might suggest inappropriate treatment or under-recording of diagnosis. The authors noted that incorporating an appropriate set of codes in the Quality and Outcomes Framework would likely improve the provision of care and recording of relevant information.

3.3 France

3.3.1 The healthcare system

Healthcare in France is largely funded through statutory health insurance, covering all legal residents. In 2009, statutory health insurance accounted for 72.5 percent of health expenditure, complemented by out-of-pocket payments (7.3 percent), taxation (5.5 percent) and voluntary health insurance (13.3 percent).[52] In the same year, total health expenditure was 11.8 percent of gross domestic product.

The Ministry of Health oversees the overall health sector while regions have an increasingly important role in healthcare provision through the regional health agencies (*agences régionale de santé*, ARSs), established in 2010. The ARSs have responsibility for ensuring that healthcare provision meets the needs of the population by improving coordination between ambulatory and hospital care and health and social care services, while respecting national health expenditure objectives.[48]

Health services are delivered by public and private providers in ambulatory care and in hospital. GPs mainly work in private practice as self-employed professionals, with around 75 percent in health centres or hospitals in addition to their private practice.[91] GPs are reimbursed on a fee for services basis, with fees set nationally, based on agreements between professional organisations and the statutory health insurance administration. Since 2009, GPs can also enter into individual contracts with the statutory health insurance to receive additional payments rewarding practice improvements (*contrats d'amélioration des paratiques individuelles*, CAPIs) such as the management of chronic conditions.[48] Specialists are paid for based on fee for service in both private practice and private hospital settings. Specialists employed in a public hospital receive a salary.

The 2004, Health Insurance Reform Act introduced a form of gatekeeping through the preferred doctor scheme (*médécin traitant*) in the ambulatory care sector from 2005 and higher co-payments for patients accessing care outside a coordinated care pathway. The reform further created the National Authority for Health (*Haute Autorité de Santé*, HAS), an independent body which, among other things, was made responsible for the development of guidelines for the treatment of chronic diseases.

3.3.2 Country burden attributed to postmenopausal osteoporosis and associated fractures

In 2010, the French population was 62.5 million, with 17.4 percent aged 65 years and over (80 years and over: 5.3 percent).[52]

Using the French national hospital database, Maravic et al. (2005) reported, for 2001, an incidence rate for all fractures at 7,567 and 2,312 per 1,000,000 population for, respectively, women and men aged over 45 years.[92] The median inpatient costs were estimated at around €2,500 for radius fractures and around €8,400 for hip fractures. More recently, Maravic et al. (2010) showed that the incidence of hip fracture in women aged 40 years and over in France has remained stable from 2002 to 2008 with around 50,910 hip fractures annually.[93] Hip fractures were found to be associated with a 20 percent mortality rate for women aged 50 years and older.[94]

Further analysis of the national hospital database documented an increase in the absolute number of hospitalisations for wrist fractures, from 38,710 in 2002 to 38,979 in 2006 (both sexes combined).[95] These fractures were associated with total in-patient costs of €79 million in 2006 (at an average individual cost of €2,100 per hospitalised wrist fracture). There are also between 40,000 and 70,000 vertebral fractures per annum.[94]

Analysing data from nine cohort studies undertaken in France, Amamra et al. (2004) estimated that 30 percent of women over the age of 50 years may have at least one risk factor for osteoporosis and that about 7.4 percent of these women had at least two risk factors for the condition.[96] These estimates need to be interpreted with caution as the study sample was not representative of the population in France, although the size of the sample (just under 124,000 women) and the diversity of data sources supports their validity. More recently, Roux et al. (2008), using a cross-sectional survey of osteoporosis in post-menopausal women aged over 45 years in the general population, found that of the 2,081 women interviewed, 52 percent reported at least one risk factor for osteoporosis.[97] About 18 percent reported multiple risk factors and the proportion of those doing so increased with age. Using the same data, Lespessailles et al. (2009) estimated the prevalence of diagnosed osteoporosis among women over 45 years in France to range between 8.6 percent and 10.9 percent (point estimate: 9.7 percent).[98]

3.3.3 Strategies and guidelines for osteoporosis

In France, while there is no explicit governmental strategy to address osteoporosis, healthy ageing and limiting dependency have been identified as priorities. This includes enabling older people who are dependent to remain at home with appropriate support if they so wish and supported self-management of chronic conditions. These priorities have been described in a number of strategy documents such as the 2006 *Plan Solidarité – Grand Age*,[99] the 2007 *Plan national 'bien vieillir' 2007–2009*[94] and the 2007 *Plan pour l'amélioration de la qualité de vie des personnes atteintes de maladies chroniques*.[100] The *Plan Solidarité* identified osteoporosis as a condition contributing to older people becoming dependent and proposed GP consultations free of charge for those aged over 70 years from 2007 to facilitate early diagnosis and prevention.[99] The plan on the quality of life for people with chronic disease specified a target for a reduction of 10 percent of hip fractures by 2008.[100] However, it did not specify how this should be achieved in practice.

There are a two sets of national guidelines in place in France: those issued in 2006 by the national health authority, the HAS[101] (see below), and those issued by the agency for the safety of medicinal products, Agence française de sécurité sanitaire des produits de santé (Afssaps), also in 2006 and updated in 2008.[102] The aims of the guidelines issued by Afssaps were to provide a best practice guide for the treatment and prevention of post-menopausal osteoporosis and to prevent fractures in a five- to ten-year span.

According to French key informant, Afssaps has resisted updating its guidelines despite calls from experts to do so, mainly because of concerns about conflict of interest. In response, a group of experts representing the French Society of Rheumatology and the GRIO (Research and Information Group on Osteoporosis) have begun drafting new guidelines, which are expected to be presented at the end of 2011 and are being reviewed by the scientific societies.

3.3.4 Financing and managing postmenopausal osteoporosis

Until 2006, DXA measurement and treatment were not reimbursed under the statutory system unless the patient had already sustained one fracture. However, the 2006 guidance by the HAS introduced, for the first time, systematic reimbursement for densitometry in postmenopausal women presenting with specific risk factors for osteoporosis or osteoporotic fracture as well as for specific osteoporosis therapy for those with low bone mass density.[101] Thus, treatment will be reimbursed for women with fragility fracture, postmenopausal women with a BMD T-score ≤–3 SD or in those with a BMD T-score ≤–2.5 SD plus at least two other risk factors (age ≥60 years, current glucocorticoid therapy, parental hip fracture or menopause before age 40 years).

GPs are mostly responsible for diagnosing and treating the osteoporosis in France. About 80 percent of prescriptions for osteoporosis medications are issued by GPs, with the remainder equally spread between rheumatologists and gynaecologists. There is a notion that the majority of GPs who issue prescriptions for osteoporosis medications tend to have a special interest in the condition.

3.3.5 Evidence on quality of care for postmenopausal osteoporosis

Using international sales data on prescription drugs as a proxy for treatment, Ström et al. (2011) estimated that, in France in 2008, 7.8 percent of the population aged over 50 years did take up treatment for osteoporosis.[40] They further estimated that there were 12.4 million women aged 50 years or older in France, of whom approximately 12 percent were being treated (these numbers are based on the assumption that women receive 87 percent of all prescribed treatment). Relating these figures more specifically to those with osteoporosis as defined by BMD, an estimated 53 percent of women aged 50 years and older with osteoporosis were treated for the condition. This proportion is slightly higher if related to those who exceed the fracture risk threshold for treatment, identifying a 'treatment gap' of 41 percent, implying that approximately 60 percent of those eligible for treatment do indeed receive it.

There is very little published empirical work on the quality of care in relation to the prevention and treatment of postmenopausal osteoporosis in France, which poses a challenge for the systematic assessment of the quality of the management of osteoporosis. The evidence that is available points to underutilisation of diagnosis and treatment, in particular before the introduction of the 2006 HAS guidance, with considerable improvements thereafter observed by some.

For example, Briançon et al. (2004), in a small study of 106 women aged over 50 years who had presented to their orthopaedic surgeon with their first low-impact peripheral fracture, found that 47 percent had been given a diagnosis of osteoporosis by their primary care physician while 35 percent had received medication.[103] Blotman et al. (2007), using a random sample of 389 GPs who recruited a total of just under 3,100 postmenopausal women with a diagnosis of osteoporosis, and who were followed up for a period of at least two years, found that of those women who had completed a questionnaire, 97.4 percent were receiving treatment for osteoporosis, most frequently weekly bisphosphonates.[104] However, a large proportion of women with osteoporosis (59.7 percent) were only diagnosed with the condition after they had already sustained a fracture. Thus, while treatment of osteoporosis was found to be high, diagnosis appeared to be suboptimal. The proportion of those with a diagnosis of osteoporosis to receive treatment was found to be

lower in a study by Lespessailles et al. (2009).[98] Reporting on a survey of osteoporosis in over 2,600 women over the age of 45 years, they observed that 61 percent received osteoporosis treatment, typically bisphosphonates (50.3 percent of women receiving treatment). Differences in study design are likely to explain some of the observed variation in findings.

The hypothesis that extending reimbursement of bone density measurement to a wider group of people at risk from 2006 may have led to wider uptake of DXA assessment was not confirmed by Canoui-Poitrine et al. (2010).[105] Analysing all physicians' claims for BMD testing among women aged 50 years and older in the region Rhone-Alpes, the study found that between 2006 and 2009 a much smaller proportion of women than expected had had the test compared with the potential number of eligible women who met the eligibility criteria for the test, and this proportion tended to decrease over time. Furthermore, only about a quarter of those who had had an initial densitometry received subsequent treatment with medication for osteoporosis.

Dreinhöfer et al. (2005), using a multinational survey of osteoporotic fracture management by orthopaedic surgeons, found that, in France, the majority would refer a patient with suspected osteoporosis on to an osteoporosis specialist or GP while less than 10 percent would directly initiate BMD measurement for such a patient.[77] Where patients had undergone surgery because of a fragility fracture, just under 40 percent of surgeons reported to referring the patient for BMD assessment most or all of the time. Few would prescribe bisphosphonates for those with osteoporosis and less than half would prescribe calcium and vitamin D. Importantly, while the majority of respondents believed that they should identify and initiate the assessment of osteoporosis in patients with fragility fractures, only about 25 percent reported feeling knowledgeable about managing the condition.

Overall, the available evidence appears to point to suboptimal care delivered to postmenopausal women at risk of osteoporotic fractures, with a perceived need for improvements in the diagnosis of osteoporosis in particular, as well as the steps taken when a patient is identified as having a low BMD. Conversely, calcium and vitamin D appear to be widely prescribed in France with GPs having begun to carry out vitamin D assessments more systematically and so many patients with low levels of BMD are now given supplements.

Under-diagnosis might reflect challenges in accessing diagnostic equipment such as DXA measurement. However, as noted before, the criteria for those potentially eligible for bone density measurement have been extended in 2006. Furthermore, France is among those countries with a high density of DXA equipment, exceeding the recommended ratio of 10.6 DXA units per million population, at 29 units/million population in 2010.[40] The observations presented here suggest that quantity or density of DXA testing equipment does not imply use, in particular appropriate use.

There appears to be a tendency for younger women to have DXA assessment and receive treatment where necessary. However they would have to pay for the test if they do not meet the criteria for reimbursement. Conversely, older women who are at greater risk of osteoporosis-related fractures do not tend to be tested in a systematic way and there appears to be a general lack of knowledge on the part of both GPs and patients about the

condition, reflecting a common perception that fractures are an inevitable feature of the ageing process. Furthermore, GPs appear to find it difficult to understand the conditions under which DXA testing is covered under statutory health insurance. There are some efforts by the Research and Information Group on Osteoporosis (GRIO) to provide more information on the condition through meetings and conferences for GPs, which, combined with high quality guidelines, are expected to contribute to the overall quality of care.[106]

3.4 Germany

3.4.1 The healthcare system

The German health system is financed mainly from statutory health insurance. The statutory health insurance system covers about 90 percent of the population; the remainder have taken out substitutive voluntary health insurance. In 2009, statutory health insurance accounted for 68.1 percent of health expenditure, complemented by out-of pocket payments (13.1 percent), taxation (8.7 percent) and voluntary health insurance (9.3 percent).[52] In the same year, total health expenditure was 11.6 percent of gross domestic product. Since 2009, all residents are required to take out health insurance.

In the German federal system, regulation of healthcare is shared between the federal government and 16 state governments, with many tasks delegated to corporatist actors at various levels of administration as set out in legislation. The Joint Federal Committee (*Gemeinsamer Bundesausschuss*, G-BA) is the highest decision-making body in the statutory health insurance system. Established in 2004, the G-BA brings together payer (statutory health insurance funds) and provider associations, with patient representatives in an advisory role; its mandate includes defining the publicly financed benefits package and setting quality standards for ambulatory, inpatient and inter-sectoral health care.[107]

Healthcare services are provided through a mix of public and private providers. Ambulatory care is mainly provided by office-based primary and specialist care physicians who have been granted a monopoly to provide care outside hospital; patients generally have free choice of any provider in the ambulatory care sector, and some choice of hospital upon referral. Since 2007, statutory health insurance funds are required to offer GP-centred care plans (GP contracts, a form of gate-keeping), in which members agree always to seek care through their family physician first. Hospitals are public, private for-profit and private not-for-profit.

Office-based physicians are principally reimbursed on a fee-for-service basis, using a nationally negotiated scale (*Einheitlicher Bewertungsmaßstab*, EBM). Since 2009, a target volume is set for each practice, reflecting medical specialty and the number and age of patients (de facto a form of morbidity adjusted capitation payment). If services delivered in a given period exceed the target, any additional services provided are reimbursed at a lower rate. Hospital physicians and most physicians working in medical care centres are salaried.

3.4.2 Country burden attributed to postmenopausal osteoporosis and associated fractures

In 2010, the population in Germany was 82.8 million, with 20.4 percent aged 65 years and over (80 years and over: 5.1 percent).[52]

Häussler et al. (2007) estimated the prevalence, treatment and cost of osteoporosis and osteoporotic fractures in Germany.[108] Using claims data from one health insurance fund covering 1.5 million beneficiaries they calculated that, in 2003, there were 7.8 million people aged 50 years and older with osteoporosis (prevalence rate: 26 percent). Prevalence increased with age, with just under 60 percent of women over the age of 75 years estimated to be affected by osteoporosis. They further estimated that of those with osteoporosis, 4.3 percent experienced at least one fracture, most commonly of the hip (30 percent), wrist

(12.6 percent) and vertebra (12.2 percent). Recognition of osteoporosis as underlying cause of fracture was found to be low however, with only 9.7 percent of patients seen by an orthopaedic surgeon diagnosed with the condition.

The total costs attributable to osteoporosis were estimated at €5.4 billion (or 3.5 percent of all healthcare expenditure within the statutory health insurance system) in 2003. Just over half of the costs (56 percent) were in the inpatient sector, followed by long-term care (nursing) (18 percent) and medication (15 percent). The largest medication category was analgesic drugs, at 62.9 percent, with osteoporosis-specific medication accounting for the remainder (bisphosphonates: 22.7 percent). Patients with fractures, although representing only 4.3 percent of those with osteoporosis, accounted for 61.3 percent of total cost attributable to the condition. The average cost for a person with a fracture was estimated at €9,962 compared with €281 for a person without fracture, although the latter still accounted for €882 million of inpatient cost.

Focusing on osteopenia- and osteoporosis-attributable hip fractures (OHF) specifically, Konnopka et al. (2009) estimated these to amount to just over 108,300 cases in 2002, 85 percent of which were in persons over the age of 70 years and 78 percent among women.[109] OHF cases were estimated to result in 3,485 deaths (or 22,724 years of potential life lost (YPLL)) and 17,535 QALYs lost. Of the latter, 46 percent were attributable to hip fracture. Based on current projections of future demographic trends, the authors estimated that by 2020 OHF cases would have risen by 44 percent and resultant deaths by 62 percent (YPLL: 56 percent; QALYs: 49 percent). By 2050, the number of OHF cases would have risen by 128 percent (deaths: 215 percent; YPLL: 196 percent; QALYs: 152 percent).

The overall costs associated with OHF in 2002 were estimated to be €3 billion. Of these, 91.3 percent were direct medical costs, which were mainly generated by nursing care (58.5 percent), followed by inpatient care (27.4 percent) and non-medical costs (9.1 percent). Indirect costs caused by OHF played a small role only, mostly because OHF cases are largely associated with older age with low levels of paid and unpaid productivity. Indirect costs were largely attributable to mortality, followed by sickness absence. Overall, OHF attributable costs per case ranged from €14,000 to €36,000.

3.4.3 Strategies and guidelines for osteoporosis

In Germany, there is no explicit or coherent national strategy targeting the prevention and treatment of postmenopausal osteoporosis, reflecting a notion that osteoporosis is 'not taken seriously' as indicated by the key informant for Germany. However, there are initiatives by academic and scientific associations and selected statutory insurance funds involving strategies aimed at improving the management of osteoporosis. These include the national osteoporosis guidelines developed by the Dachverband Osteologie (DVO), a joint organisation of the scientific societies in Germany, Austria and Switzerland, involved in or focused on bone research.[110]

The DVO guidelines for the prevention, diagnosis and treatment of osteoporosis were first issued in 2003, and have been updated twice since. Guideline development was based on a systematic review of the international literature, and an interdisciplinary internal and external consensus process.[110] The latter also included patient engagement, with patient groups in all three countries invited to comment on a draft guideline; the guideline is made

available in a version addressing patients as the primary audience.[111] Guideline recommendations primarily seek to optimise care processes, reduce the incidence of fractures, and enhance the quality of life and functional status of persons with fractures.[110] The primary audience are all physicians in ambulatory and specialist care as well as all other health professionals involved in the prevention, diagnosis or treatment of osteoporosis. The next update is foreseen for 2012.

Although the DVO guidelines are frequently referred to as national guidelines, it is important to note that they are not legally binding.

3.4.4 Financing and managing postmenopausal osteoporosis

In Germany, diagnosis and treatment of postmenopausal osteoporosis is typically in the ambulatory care sector, through GPs or office-based specialists. The system features a particular characteristic with regard to trauma care for patients with acute fracture; trauma surgeons are frequently the only physicians encountered by a patient with fracture so that trauma centres and departments carry a particular responsibility for diagnosis and therapy of osteoporosis.[112]

One of the key challenges posed by the German healthcare system is the strict separation between the ambulatory and hospital care sectors, although efforts have been made recently to enhance cooperation between the sectors.[113] However, this separation can lead to uncertainty about responsibilities for osteoporosis care, in particular as it relates to payment for diagnosis and treatment.[114]

In the ambulatory care sector, statutory health insurance will only reimburse diagnosis using bone density measurement and pharmacological treatment with calcium and vitamin D as recommended by the national guideline in case of 'manifest osteoporosis'. Specifically, statutory health insurance will only reimburse BMD assessment for patients with fracture and whose medical history provides sufficient evidence for suspected osteoporosis.[115] Therefore, patients without prior fracture will typically have to pay for DXA assessment out of pocket. The standard fee for DXA measurement is around €25.

Because of the reimbursement target volumes in ambulatory care described earlier, a prescribing physician might run the risk of having to cover the associated costs if they prescribe prophylactic treatment with calcium and vitamin D based on privately paid for DXA findings for those not formally eligible for treatment.

3.4.5 Evidence on quality of care for postmenopausal osteoporosis

A recent overview by Schumacher and colleagues (2007) noted a lack of representative data suitable to describe the current situation on Germany with regard to the diagnosis and management of osteoporosis and falls, in particular as it relates to diagnostics other than bone mineral density assessment using DXA measurement and treatment other than pharmacological.[116] Evidence that is available points to under-diagnosis and under-treatment using pharmacological therapies.

Using international sales data on prescription drugs as a proxy for treatment, Ström et al. (2011) estimated that in 2008 2.9 percent of the population in Germany aged 50 years did take up the treatment for osteoporosis.[40] They further estimated that there are almost 18 million women aged 50 years or older, of whom approximately 4.5 percent were being treated (these numbers are based on the assumption that women receive 87 percent of all

prescribed treatment). Relating these figures more specifically to those with osteoporosis as defined by BMD, an estimated 20 percent of women aged 50 years and older with osteoporosis were treated for the condition. This proportion is slightly higher if related to those who exceed the fracture risk threshold for treatment, identifying a 'treatment gap' of 75 percent, implying that only one-quarter of those eligible for treatment indeed receive it.

The study by Häussler et al. (2007) referred to earlier also estimated relatively low treatment rates of people with osteoporosis aged 50 years and older, with only 21.7 percent receiving osteoporosis-specific therapy (men: 12 percent; women: 34 percent).[108] Treatment prevalence fell with increasing age, from 31 percent among women aged 50–64 to 19 percent among those aged 75 and older. The most common treatment was with calcium or calcium combined with vitamin D (17 percent), bisphosphonates (10 percent) and hormone therapy (8 percent) (any osteoporotic medication: 22 percent).

Using a prospective observational design, Endres et al. (2007) evaluated the diagnosis and treatment of osteoporosis among 652 postmenopausal women aged 55 years and older who were hospitalised with sustained distal radius fracture during 2002 to 2003.[114] The study found that although low-energy fracture of the distal radius is commonly considered an early indication of osteoporotic fracture, only one-third (33 percent) of patients underwent bone density measurement while in hospital. Furthermore, although among those assessed 55 percent were diagnosed with low BMD, only 30 percent of these were prescribed osteoporotic treatment upon discharge (bisphosphonates: 11 percent). This proportion fell to 21 percent six to twelve months after discharge. The study further showed that for just under 33 percent the patient history contained data on BMD; however, while a diagnosis of BMD reduction was confirmed in all cases, of those assessed pre-admission with no indication of bone density loss, this diagnosis was found to be wrong in 41 percent of cases; instead they were diagnosed with either osteopenia or osteoporosis following assessment in hospital. For the remainder, status of bone density was unknown pre-admission; of these, 46 percent were diagnosed with osteopenia or osteoporosis.

A recent reanalysis of the data collected by Endres et al. (2007),[114] focusing on the overall quality of care provided to older patients admitted to hospital with sustained distal radius fracture (n=1,201), found that 62 percent of women and 50 percent of men had at least one documented risk factor for osteoporosis.[117] These included diagnosed reduced bone mineral density pre-admission (30 percent), one or more falls in the three months prior to admission (52 percent), prior fracture (36 percent), loss of height during preceding 20 years of over 4 cm (44 percent) and others such as low body weight, lack of dietary calcium, corticosteroid therapy, or smoking. Yet only 33.6 percent of inpatients were assessed for BMD; of these, 70 percent of those aged 75 and older were diagnosed with reduced BMD. Just over 7 percent of all patients were discharged with basic calcium or vitamin D treatment while 7.9 percent were prescribed specific medication for osteoporosis (eg bisphosphonates at 6.6 percent).

Vogel et al. (2008) assessed the use and implementation of care standards for patients with osteoporotic fractures in trauma centres and departments in Germany by the end of 2004, using a questionnaire.[112] Of those invited who also responded to the questionnaire (328/409), 35 percent reported that they followed a defined clinical pathway for patients with osteoporotic fractures. Of these, just under 30 percent (n=34) had implemented the

German national guideline for the diagnosis of osteoporosis, using DXA technology as the primary means, while 51 percent of clinics had implemented the guideline for treatment. However, only 12 percent based both diagnostic workup and therapy on the national guideline. The authors attributed the relative lack of guideline implementation by trauma centres and departments to lack of knowledge and awareness among physicians. They also noted that few clinics follow up their patients post discharge to monitor therapy, reflecting the lack of collaboration between the ambulatory and hospital care sectors, largely attributable to uncertainty about reimbursement as noted earlier.

In contrast, levels of awareness about osteoporosis appear to be high among orthopaedic surgeons. Thus, Dreinhöfer et al. (2005), using a multinational survey of osteoporotic fracture management by orthopaedic surgeons, found that in Germany, the majority (80 percent) would directly initiate BMD measurement for a patient with suspected osteoporosis.[77] Where patients had undergone surgery because of a fragility fracture, over 90 percent of surgeons reported that they referred the patient for BMD assessment most or all of the time. More than 80 percent also reported that they felt knowledgeable about managing the condition and would initiate treatment for those with evidence of osteoporosis as indicated by BMD measurement. About 90 percent would also prescribe bisphosphonates for those with osteoporosis and/or calcium and vitamin D.

There is only a little work focusing on care patterns in the ambulatory care sector. For example, Chenot et al. (2007) examined awareness among primary care physicians in Germany of osteoporosis and their knowledge and use of national guidelines for the management of this condition.[118] Based on a random sample (response rate: 41.1 percent (n=892)), the authors found self-reported competence to manage osteoporosis among physicians to be 82.7 percent, with just over half also reporting good knowledge of the national guideline. Of these, almost two-thirds reported that they used the guideline in daily practice, although 7 percent experienced difficulties in implementing it, with another 12 percent judging the guideline as in need of improvement. Just over one-fifth of primary care physicians reported not knowing the guideline. Knowledge of the guideline was found to be associated with being female, seeing more patients with osteoporosis, visiting patients in nursing homes and having access to the internet. The most frequently reported barrier to guideline implementation in practice was budgetary constraints over prescribing: the risk of being financially penalised when exceeding the annual target budget for prescribing in primary care.

Although this study indicated GPs had a relatively good rating for their awareness and competence to manage osteoporosis in practice, it also highlighted that familiarity with national guidance is suboptimal. Furthermore, the authors caution that the findings might overestimate 'true' awareness, with those participating in the survey more likely to be interested in the subject area and thus have higher knowledge about it at the outset.[118] Furthermore, findings were based on self-report and actual competence was not assessed; it is likely that study participants over-reported on awareness, competence and guideline knowledge as a desirable feature.

In summary, available evidence indicates considerable levels of under-assessment of bone density among people at risk as well as under-treatment of those diagnosed with osteoporosis in Germany. However, it should be noted that much of the work presented

here reflects the situation in the early 2000s and both diagnosis and treatment are likely to have improved since. For example, Vogel et al. (2008) reported that, according to earlier data from the mid-2000s, Germany had had a comparatively low density of DXA units compared with other countries and the recommended density of 10.6 DXA units per million population;[40 112] however, a more recent assessment found density of DXA units in Germany to have doubled since, to 21.1 units per million population in 2010.[40] Yet quantity or density of DXA testing equipment does not imply use, in particular appropriate use. For example, there appears to be a tendency among younger women to have DXA assessment although they may not necessarily be at risk. Conversely, older patients from age 70 years and more who do not meet the criteria set by the statutory health insurance system because of not having sustained fracture are less likely to have a DXA assessment undertaken privately (pay out of pocket) even though they have an increased fracture risk because of their age.

3.5 Spain

3.5.1 The healthcare system

The Spanish national health system (*Sistema Nacional de Salud*, SNS) is tax-funded, provides universal coverage and predominantly operates within the public sector.[50] In 2009, taxation accounted for 69.1 percent of total health expenditure, complemented by a small contribution of social security payments (4.6 percent), out-of-pocket payments (20.1 percent) and voluntary health insurance (5.4 percent).[52] Healthcare provision is free of charge at the point of delivery except for a 40 percent co-payment for prescribed pharmaceuticals required for all under the age of 65 years. In 2009, health expenditure constituted 9.5 percent of gross domestic product.[52]

The national Ministry of Health and Social Policy is the guarantor of the equitable provision of health services; the highest body for the SNS is the Inter-territorial Council of the National Health System (*Consejo Interterritorial del Sistema Nacional de Salud*, CISNS), which brings together the 17 regional ministers of health, chaired by the national minister. The regions (autonomous communities) are responsible for organising and regulating healthcare delivery, overseen by central government. Regional governments typically divide the responsibility for health between a regional ministry of health, tasked with health policy and planning, and the regional health administrations, responsible for the organisation and delivery of health services. Regional health policy is to some extent coordinated between regions through the CISNS.

Regional health systems typically comprise healthcare areas, responsible for primary and secondary care, and basic health zones, which form the smallest unit of organisation, typically organised around a primary care team. Private hospitals and hospitals run by local administrations may also provide services to the regional SNS.[50]

In the SNS, GPs typically work in health centres. Most specialists are based in hospital, with the exception of those working in primary or ambulatory care settings (e.g. dentists, stomatologists, paediatricians). Specialised ambulatory care is largely provided in community polyclinics, which are typically associated with a hospital. All health professionals in the SNS are paid a salary and most have special public servant status. GPs typically receive a salary and a capitation payment, based on the characteristics of the population served. Hospital doctors and specialists in ambulatory settings also receive a salary. Extra billing is not permitted within the public sector.

3.5.2 Country burden attributed to postmenopausal osteoporosis and associated fractures

Similar to other European countries, the Spanish population is ageing. In 2010, of a total population of 46.8 million, 17 percent were aged 65 years and over (80 years and over: 5 percent).[52]

Álvarez (2002) estimated that, in 2002, there were about 3 million people with osteoporosis, of whom 2.5 million were women.[119] However, only about 18 percent of these women had been diagnosed with the condition. Using a retrospective analysis of the use osteoporosis medications from 1986 to 2000 across Spain, García del Pozo et al. (2004) found a 16-fold increase in the use of calcitonin, bisphosphonates and raloxifen

from 0.14 DDD/1,000 population per day to 4.91 DDD/1,000 population per day.[120] This increase was explained, largely, by a rise in the number of postmenopausal women most at risk of developing the condition although some of the increase may be attributable to inappropriate prescribing because of challenges in diagnosing osteoporosis accurately. In either case, associated costs were estimated to be high, at €156 million in 2002, with calcitonin accounting for 53 percent, bisphosphonates for 28 percent and raloxifen for 19 percent.

Other evidence also reported an increase in the annual number of hip fractures, rising from 7.6 per 10,000 population in 1998 to 15.7 per 10,000 population in 2006.[121] Associated costs are estimated to be high. For example, Bouza et al. (2007) analysed the national hospital discharge register records for all osteoporosis-related vertebral fractures in the Spanish population aged over 30 years (7,100 records).[122] Their analysis found that, in 2002, the associated average length of hospital stay was 11.4 days and that direct inpatient costs exceeded €41 million, equating to 0.1 percent of expenditure on hospitalisations and specialised care in Spain. Other work has estimated the direct individual hospital cost attributable to hip fracture to have increased between 2001 and 2007, from €5,000 to between €7,500 and €8,000.[121]

3.5.3 Strategies and guidelines for osteoporosis

We were unable to identify documented evidence of an overarching strategy at the national-level targeting, directly or indirectly, the prevention and treatment of postmenopausal osteoporosis.

In 2001, the Spanish Society for Bone and Mineral Research (*Sociedad Española de Investigación Ósea y del Metabolismo Mineral*, SEIOMM) issued national guidelines on osteoporosis that were updated in 2008.[123] The guidelines cover individuals with osteoporosis (postmenopausal women; men) and with steroid-induced osteoporosis (women). They guidelines broadly recommend a case finding approach to identify those who should be tested using bone densitometry, based on the presence of risk factors including age, previous fracture and clinical risk factors. They are targeted primarily at primary care clinicians and specialised clinicians involved in the medical treatment of osteoporosis and provide recommendations for the establishment of protocols and assist clinical practice.

3.5.4 Financing and managing postmenopausal osteoporosis

In 2002, the diagnosis and treatment of patients for osteoporosis was fully reimbursed for those over 65 years, whereas for those at younger ages the SNS only covered 40 percent of treatment and diagnosis cost.[119] At that time, Spain was one of a few EU countries where full reimbursement of diagnosis and treatment was accessible to the target population. More recently, Ström et al. (2011) noted that reimbursement has remained unrestricted for both DXA assessment and treatment although access to DXA may be unequal across some parts of the country.[40]

Available evidence suggests that the majority of patients with osteoporosis in Spain are not being managed in the primary care setting, with Ciria et al.(2000) estimating this to be the case for about 28% of those with osteoporosis.[124] A 2001 postal survey of 850 primary care physicians across Spain found that over half of patients (53 percent) were referred to a specialist for diagnosis and treatment by their GPs.[125] Furthermore, only a small number of

GPs (4 percent) reported working in a primary care centre that had implemented specific programmes for the management of osteoporosis.

3.5.5 Evidence on quality of care for postmenopausal osteoporosis

Using international sales data on prescription drugs as a proxy for treatment, Ström et al. (2011) estimated that in Spain in 2008 10.7 percent of the population aged 50 years did take up the treatment for osteoporosis.[40] They further estimated that there were 8.5 million women aged 50 years or older in Spain, of whom approximately 16 percent were being treated (these numbers are based on the assumption that women receive 87 percent of all prescribed treatment). Relating these figures more specifically to those with osteoporosis as defined by BMD, an estimated 72 percent of women aged 50 years and older with osteoporosis were treated for the condition. This proportion is slightly higher if related to those who exceed the fracture risk threshold for treatment, identifying a 'treatment gap' of 19 percent, implying about 80 percent of those eligible for treatment indeed receive it.

These observations have to be set against other evidence, which highlights that only a small proportion of women with osteoporosis are being diagnosed and subsequently treated for this condition in Spain. For example, in 2002, the Spanish Foundation of Osteoporosis and Metabolic Bone Disease estimated that 80 percent of women with osteoporosis were not aware of the risk factors for this condition before diagnosis and only 10 percent were found to receive treatment for it.[119]

In addition, there is some evidence of overtreatment in that some women receive medication while not having been diagnosed with osteoporosis, or having one or more critical risk factors for the condition. For example, in 2008, a survey of 332 women aged 45 years or over receiving treatment for osteoporosis found that although 73 percent had one or more risk factors related to osteoporosis, over one-quarter presented no risk factors at all.[126] The study also reported that of all women treated for the condition, only about 60 percent had undergone densitometry. For the most part, BMD measurement was requested by specialists such as gynaecologists and traumatologists, while in only 12 percent of cases requests originated from a primary care physician. In addition, 42 percent of densitometry tests were carried out in private clinics although diagnostic testing is reimbursed under the public system.

Importantly, the analysis by Arana-Arri et al. (2008) noted that almost 60 percent of those receiving osteoporosis treatment did not present risk factors for the condition and had undergone densitometry testing whereas 40 percent of those presenting risk factors for the condition had not.[126] It is worthwhile noting that about two-thirds of women studied were found to have had their treatment initiated by a traumatologist or gynaecologist, and in 60 percent of cases, treatment initiation was based on diagnostic testing. However, of these, 42 percent showed evidence of inappropriate dosing. Treatment mostly (59 percent) involved bisphosphonates and calcium or vitamin D supplementation.

In their population-based study using hospital discharge data for all osteoporosis-related vertebral fractures in the Spanish population aged over 30 years, Bouza et al. (2007) noted that in only 35 percent of cases was a diagnosis of osteoporosis explicitly mentioned, supporting a general perception of osteoporosis being 'ignored' in the hospital setting and not reflected in medical records.[122]

This latter point is somewhat in conflict with the findings of a survey among orthopaedic surgeons. Thus, Dreinhöfer et al. (2005), using a multinational survey of osteoporotic fracture management by orthopaedic surgeons, found that in Spain, almost two-thirds (60 percent) reported that they regularly prescribed osteoporosis medication (for one to ten patients per month).[77] In addition, more than half (57 percent) believed it to be their responsibility to treat patients with osteoporosis, about 80 percent reported feeling knowledgeable about managing the condition, and 60 percent would directly order BMD measurement for those with suspected osteoporosis.

There is some notion of potential problems in accessing adequate equipment for the diagnosis of osteoporosis in Spain, with evidence of low levels of access to DXA equipment among primary care physicians in the early 2000s.[119] A 2001 survey of 850 primary care physicians across Spain also noted that only about 27 percent of those surveyed reported that they could order bone densitometry compared with 96 percent to be able to do so for radiographs.[125] A recent assessment reported that the density of DXA units in Spain has remained low, at an estimated 8.4 units per million population, which is below the recommended service guideline threshold of 10.6 DXA units per million population.[40] Therefore, although quantity or density of DXA testing equipment does not imply use, especially appropriate use, access to BMD measurement equipment appears to remain a challenge in the Spanish healthcare system.

Several sources point to a lack of knowledge of and training in the management of osteoporosis among primary care physicians in particular. The aforementioned survey of 850 primary care physicians by Pérez-Edo et al. (2004) found that self-reported knowledge about the condition decreased with age and years of practice.[125] These observations point to a need to improve education about osteoporosis, alongside interventions supportive of enhancing knowledge and the diagnosis and documentation of osteoporosis risk factors in primary care. Orozco (2005) suggested that lack of specific training and knowledge makes it difficult for GPs to make use of information on the condition, and difficulties to access bone densitometry testing equipment may reduce their interest in learning about the condition because they are often unable to diagnose it.[127] The survey by Arana-Arri et al. (2008) of women receiving treatment for osteoporosis concluded that there are important deficiencies in both the diagnosis and treatment of osteoporosis partly because of a lack of access to densitometry testing equipment, and possible deficiencies in training or awareness-raising on the prevention and diagnosis of the condition in all medical specialties.[126]

Taken together, available evidence points to a complex picture of the prevention, diagnosis and treatment of osteoporosis and related risk factors in Spain; there is evidence of fairly high levels of treatment compared with other European countries, with a possibility of overtreatment, while access to bone densitometry units appears to be low. However, it should be noted that the majority of studies reviewed here reported on data collected before or during the early 2000s and it remains uncertain whether and to what degree this evidence reflects the current management of osteoporosis among postmenopausal women in Spain.

3.6 Summary of country experiences

This chapter has reviewed current approaches and practices to managing postmenopausal osteoporosis in England, France, Germany and Spain, with a particular focus on the quality of care provided to those with the condition and associated fractures.

Table 3.2 provides a summary overview of the main features of the management of osteoporosis in the four countries under review. We find that both England and France have instituted overarching strategies at the national-level targeting older people and, within this, osteoporosis associated fractures and fracture risk specifically. We were unable to identify similar documented national-level strategies for Germany or Spain.

However, all countries have introduced national-level guidelines. The extent to which these are implemented and/or adhered to varies, determined, in great part, by whether diagnosis and/or treatment is being reimbursed under the statutory system as well as awareness of the guidance among professionals concerned with the management of the condition.

It may be worthwhile noting that in England, France and Germany, patients with osteoporosis are managed primarily in the primary or ambulatory care setting, while in Spain, primary care physicians tend to be less involved. The degree to which other medical specialists are involved in, and feel responsible for, the management of the condition varies among countries. For example, orthopaedic surgeons in France have been reported not to feel confident in treating osteoporosis while among those in the UK there appears to be some level of uncertainty as to the prime responsibility for managing the condition. In contrast, in Germany and Spain, orthopaedic surgeons would consider managing osteoporosis within their remit. However, these observations are based on one comparative study only[77] and further work would be required to confirm their validity.

Table 3.2 Summary overview of main features of the management of postmenopausal osteoporosis in four countries

England (UK)	France	Germany	Spain
Overarching (national) strategy to address postmenopausal osteoporosis in place			
Strategic focus on older people within National Service Framework for Older People (2001) with an emphasis on the prevention of conditions that affect older people	Strategic focus on older people within the 2006 plan on old age; the 2007 plan on healthy ageing and the 2007 plan on the quality of life of people with chronic disease	No national strategy; various initiatives by academic and scientific associations and selected statutory insurance funds	Uncertain; not documented
Existence of national/regional guidelines for the diagnosis, prevention and/or treatment of postmenopausal osteoporosis (year issued/last updated)			
(a) National Institute for Health and Clinical Excellence (NICE) *Scope:* primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women (2010/2011) (b) National Osteoporosis Guideline Group (NOGG) *Scope:* diagnosis and management in postmenopausal women and men from age 50 years (2010)	(a) National Health Authority (HAS) *Scope:* Prevention, diagnosis and treatment of osteoporosis generally (2006) (b) Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) *Scope:* medical treatment of post-menopausal osteoporosis (2008)	Dachverband Osteologie (DVO) (joint organisation of scientific organisations on bone research in Germany, Austria and Switzerland) *Scope:* prevention, diagnosis and therapy of osteoporosis in adults (2009)	Spanish Society for Bone and Mineral Research (SEIOMM) *Scope:* prevention, diagnosis and therapy of osteoporosis in adults (2008)
Funding arrangements			
Access to DXA assessment and treatment free of charge for those meeting eligibility criteria set out by NICE guidance	Full reimbursement for densitometry in postmenopausal women with risk factors for osteoporosis or osteoporotic fracture as well as for specific osteoporosis therapy for those with low bone mass density	In the ambulatory care sector, the statutory system will only reimburse BMD assessment for patients with fracture and whose medical history provides sufficient evidence for suspected osteoporosis	Full reimbursement of diagnosis and treatment of patients for osteoporosis for those aged over 65 years; for those at younger ages, the Sistema Nacional de Salud (SNS) only covers 40 percent of treatment and diagnosis cost
Providers involved in the diagnosis, prevention and treatment of osteoporosis			
General practice, rheumatology, orthopaedics, endocrinology, metabolic medicine, geriatrics, and obstetrics and gynaecology GPs can contract for 'enhanced services' relating to the diagnosis and prevention of osteoporosis involving additional payments upon meeting defined criteria	GPs are the principal provider responsible for diagnosis and treatment; other specialties involved include rheumatologists and gynaecologists	Diagnosis and treatment of postmenopausal osteoporosis is typically through GPs or office-based specialists in the ambulatory care sector. Other specialties involved include surgeons in trauma centres or departments	Diagnosis and treatment is mostly through specialists such as gynaecologists, traumatologists and orthopaedic surgeons

Table 3.3 presents selected indicators of the burden of osteoporotic fractures and related treatment in four European countries, based on analyses recently presented by Ström and colleagues (2011) that were derived from sales data on prescription drugs for the treatment of osteoporosis alongside estimates of the population at risk based on a simulation model.[40]

Table 3.3 Selected indicators of the burden of osteoporotic fractures and related treatment in four European countries

	UK	France	Germany	Spain
Lifetime probability of a major osteoporotic fracture in women aged 50+	36	35.9	31.4	25.5
Number of women aged 50+ with osteoporosis as defined by BMD T-score <=2.5 SD (000)	2,545	2,817	4,034	1,937
Proportion of osteoporotic population potentially treated (%)	*40*	*53*	*20*	*72*
Number of women aged 50+ exceeding fracture risk threshold (000)	2,363	2,514	3,301	1,722
Proportion receiving treatment (%)	*44*	*59*	*25*	*81*

SOURCE: adapted from Ström et al. (2011)[40]

Figures presented in Table 3.3 point to a relative 'ranking' of countries in relation to the treatment of women aged 50 years and more with osteoporosis or at risk of fracture. The estimates place Germany at one end of the spectrum with relatively low treatment rates, with between one-fifth and one-quarter of women potentially eligible for treatment, and Spain at the other end, presenting almost a mirror-image of data for Germany. England and France are somewhere in the middle of the spectrum.

Estimates for France shown in Table 3.3 appear to correspond well to other data sources reported on in our review, while those for England suggest slightly higher treatment rates, in the region of 50 percent to 60 percent, depending on the setting.[85 89-90] Available evidence on treatment rates in Germany points to low treatment levels, concurring with the estimates presented by Ström et al. (2011),[40] although it should be noted that the figures for Germany presented in our review tend to reflect treatment patterns of the early 2000s.[108] In contrast, treatment rates in Spain are estimated to be high and we have identified some evidence supporting this notion. A recent analysis of the Global Longitudinal Study of Osteoporosis in Women (GLOW) found that women aged 55 years and more in southern Europe (four centres in Spain, France and Italy) were two times more likely to receive pharmacological treatment for osteoporosis than those in northern Europe (four centres in Belgium, Germany, Netherlands and the UK).[128] However, some findings also point to possible overtreatment, highlighting evidence of women being treated despite not having been diagnosed with osteoporosis or having one or more critical risk factors for the condition.[126] The work by Ström et al. (2011) identified Spain as one of six EU countries (France, Germany, Italy, Spain, Sweden and the UK) with the highest estimated sales of prescription drugs for the treatment of osteoporosis.[40] Yet the lifetime probability of a major osteoporotic fracture in women aged 50 years and more is estimated to be lower than, for example, in England, France and Germany (Table 3.3), which may or may not reflect possible overtreatment.

Importantly, in all countries reviewed here, there is evidence of under-diagnosis and available literature points to a number of challenges faced by practitioners to implement guidance. For example, in France, the density of diagnostic equipment to assess bone density (DXA scans) has risen and is now relatively high in comparison with other European countries.[40] Furthermore, eligibility criteria for reimbursement for DXA scans have been extended in 2006. Yet uptake of DXA measurement appears to have remained stable at low levels. This has been explained, in part, by GPs finding it difficult to understand the conditions under which DXA testing is reimbursed under the statutory system. In Germany, uncertainty about responsibilities and payment between the ambulatory and hospital sector have been described as the main barriers for implementing guidelines in practice, with challenges of reimbursement in ambulatory care possibly acting as a disincentive to a more systematic approach to diagnosis. In Spain, low levels of awareness and knowledge among primary care physicians have been identified as one key barrier, with restricted access to DXA scans also an important factor for under-diagnosis.

Improved information on reimbursement modalities and clarification of responsibilities for the management of osteoporosis and associated fractures and communication between sectors are likely to go some way to enable a more systematic approach to addressing the related societal burden in European populations. In England, limited experiments with the use of fracture liaison services bridging primary and specialist care showed how these might enhance referral for BMD measurement following fracture and/or treatment. Recent evidence from France also indicated how such services may support adherence to treatment by patients.[129] However, despite the potential benefits, such services have not been implemented widely.

Overall, we observe a complex picture with regard to current approaches to and practices for managing postmenopausal osteoporosis in England, France, Germany and Spain. However, observations had to draw, to a considerable extent, on a rather patchy evidence base, often relying on studies of small samples and/or single providers and with little systematic data collection. Furthermore, evidence that is available frequently relates to data collected in the early 2000s, so findings reported here have to be interpreted with caution.

The relative lack of sound evidence indicates there is considerable need for the establishment of routine monitoring systems to enable better understanding of contemporary patterns and trends and to identify care gaps in the management of this condition. The 2007 'Evaluation of Standards of Care for Osteoporosis and Falls in Primary Care' in the English NHS was able to draw on electronic medical records.[89] This enabled not only a more systematic assessment of current practice of osteoporosis management in primary care but also the identification of avenues for further enquiry, for example as to whether an observed prescription rate for osteoporosis treatment for patients without a documented diagnosis was attributable to inappropriate treatment or under-recording of diagnosis. Such analyses are crucial to inform targeted strategies and policies to address the burden of osteoporosis and associated fractures effectively.

Part III. Informing the development of quality indicators for the management of postmenopausal osteoporosis

CHAPTER 4

Informing the development of quality indicators for the management of postmenopausal osteoporosis

This report set out to inform the development of quality indicators for postmenopausal osteoporosis management through (a) assessing the evidence for the screening and diagnosis of osteoporosis and related risk factors, and for the prevention and treatment of osteoporosis and osteoporosis-related fractures and (b) describing current practice for managing postmenopausal osteoporosis in Europe.

We presented two sets of analyses: first, a comprehensive review of reviews of the peer-reviewed and grey literature for the screening and diagnosis of osteoporosis and related risk factors, and for the prevention and treatment of osteoporosis and osteoporosis-related fractures; second, a review of current approaches and practices to managing postmenopausal osteoporosis by means of country case studies of England, France, Germany and Spain, with a particular focus on the quality of care provided to those with the condition and associated fractures.

We find that there is good evidence on the effects of selected treatments on clinical outcomes of postmenopausal osteoporosis and associated fractures, and on the usefulness of selected simple risk factor assessment tools to identify postmenopausal women who would benefit from further diagnostic assessment, such as DXA measurement. However, uncertainties remain in a number of related areas. These include the optimal use (frequency, quantity, duration) of pharmacological interventions for preventive purposes; of the combinations of pharmacological and/or non-pharmacological interventions that may prevent any type of fracture; of specific populations which would benefit from a given intervention or have not been studied; and the effectiveness of population-based screening. The available evidence does however provide a basis to inform quality improvement in clinical practice and has led to the development of clinical guidelines in many settings in Europe.[40 66-67 69 72 101-102 110 123] Yet, as we have also shown, available evidence points to considerable levels of under-diagnosis and under-treatment of osteoporosis and associated fractures in European countries, even where relevant guidelines for clinical practice have been instituted.

We have identified a considerable need for the better understanding of current approaches and practices to managing postmenopausal osteoporosis in European settings to enable identified care gaps in the management of this condition to be addressed and so improve the overall quality of care of those with osteoporosis and associated fractures. This chapter

aims to embed these observations into a broader discussion on the development and use of quality indicators for the management of postmenopausal osteoporosis. We begin by briefly outlining the conceptual and methodological considerations regarding the measurement of healthcare quality and the development of quality indicators; then we reflect on existing quality indicators for osteoporosis currently in use. We close by considering how the evidence we have presented in this report may help advance the development of quality indicators for the management of postmenopausal osteoporosis in European settings as a measure of quality improvement.

4.1 Measuring healthcare quality

4.1.1 Defining quality indicators

This section summarises the published evidence on the development and use of quality indicators, principally drawing on our previous work in this area.[51 130]

Measuring the quality of care has become an increasingly important component of quality improvement efforts, as a means to monitor effectiveness, protect patient safety, inform decision-making and ensure value for money, among many other purposes.[131] However, identifying meaningful measures suitable to capture the quality of care remains challenging.[132] This is in part related to the various ways in which healthcare quality has been defined. A widely used definition is that provided by the US Institute of Medicine, which states that quality is 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current medical knowledge'.[133]

Donabedian (1980, 1988) suggested that healthcare can be evaluated according to structure, process and outcome, as 'good structure increases the likelihood of good process, and good process increases the likelihood of good outcome'.[134-135] This approach has subsequently been adopted widely in health services research and has been used to guide the development of measures that address all aspects of quality.

As with the term 'quality', the term 'quality indicator' has been defined in different ways.[131 136-137] The common notion is that an observed change in a given indicator reflects a change in the underlying healthcare delivery and in quality of care.[138] This implies that indicators should meet certain criteria to allow for appropriate conclusions about cause and effect to be drawn and/or a course of action taken. In other words, the evidence needs to demonstrate that implementing a particular action leads to some desired outcome, for example lower morbidity.

Analysts have therefore developed a range of explicit attributes or evaluation criteria to guide indicator selection decisions, with validity (the extent to which the measure captures the concept it is meant to measure), reliability (the extent to which measurement with the given indicator is reproducible) and sensitivity to change considered among the key criteria,[130] while some authors have proposed up to 12 attributes.[139] More recently, there has been a move to consolidate the wide range of attributes into four core evaluation criteria:[51]

a) Importance: does the indicator provide information on a topic of relevance to decision-makers?

b) Scientific soundness: does the indicator capture the underlying construct in a reliable and valid way, and is it based on evidence or solid professional consensus?

c) Feasibility: is it possible to collect data for the indicator with reasonable effort?

d) Usability: can the indicator provide actionable information for decision-makers?

The most detailed operational definitions for these criteria are currently maintained by the National Quality Forum (NQF),[140] which are widely used in the United States and elsewhere.

4.1.2 Process or outcome measures?

An important consideration for the design of quality indicators is the level at which assessment takes place. This can range from the primary process of patient care (micro level) to the organisational context (meso level) to the financing and policy, or health sector context within the wider health system (macro level).[141]

A further consideration is whether to use process and/or outcome measures to assess the effectiveness of healthcare;[134-135] while most approaches to quality assessment tend to use a combination, the debate on the relative usefulness of either is ongoing.[142]

Process measures offer an important tool for assessing the current quality of care being delivered; they are useful for evaluating whether interventions have led to improved quality.[143] For example, process indicators tend to be more sensitive to changes in the quality of care and provide a clear direction to identify what needs to be done differently to improve care delivery; they are easily measured and interpreted, and they enable detection of deficits in care more rapidly as care processes occur more frequently.[138 142-143] Yet as process indicators tend to focus on a given intervention or condition there may be a need for a range of measures to assess the quality of care for a particular group of patients. Importantly, process indicators can easily be manipulated, potentially undermining quality improvement efforts.

Outcome measures focus 'the attention of policy-makers on whether systems are achieving the desired goals'.[144] However, the outcomes of interest are often (much) delayed and it is thus difficult to establish a clear link to a given intervention.[145] One example is the use of survival data to monitor the outcomes of cancer care. Also, there may be challenges to attribute observed change as it is not always clear why outcomes are poor and it may require collection of process measures to identify steps that should be taken to improve outcomes.

Mant (2001) noted that the relevance of outcome measures is likely to increase with the broadening of the perspective, towards macro-level assessments of quality.[142] This is because such measures tend to reflect the interplay of a range of factors, some of which are directly related to healthcare, and these factors are more easily addressed at the national or system level. Conversely, at the organisational or individual team level, process measures will become more useful as broader outcome measures are less easily influenced at this level.

4.2 Quality indicators for the management of osteoporosis currently in use

This section provides a brief overview of indicators that are currently in use to measure the quality of care provided to postmenopausal women with osteoporosis or associated fractures. The overview is for illustrative purposes only; we do not aim to review all potentially existing measurement systems or to provide a critical assessment of the advantages and disadvantages of indicators in use. We principally draw on indictor sources in place in the United States, informed by our earlier work on quality indicators, which demonstrated that related work is more developed in the United States than elsewhere.[51]

In the United States, the Assessing Care of Vulnerable Elders (ACOVE) project was among the first to systematically develop a set of quality indicators for the medical care provided to vulnerable older people, which also included indicators for the management of osteoporosis.[146] The ACOVE project was originally set up in 1998, with the ensuing list updated and revised twice since.[147] Indicators were developed using a structured process, involving a review of the available evidence and guidelines, alongside expert panel consideration.[148] Indicators were conceptualised as process indicators largely to facilitate measurement in daily practice and because process measures are considered amenable to direct action by providers of care. They were constructed in a *if* (clinical characteristic of the patient) – *then* (care process (not) to be performed) – *because* format (expected health effect of care provided).[147]

The 2006 revised list includes 236 indicators addressing 22 clinical conditions; for osteoporosis, of an initial 19 potential quality indicators, 13 were judged as valid by the expert panel.[149] Table 4.1 lists the 2006 ACOVE quality indicators for the management of osteoporosis; for completeness, we also list those specifically targeted at men with osteoporosis.

Table 4.1 ACOVE quality indicators for the management of osteoporosis in vulnerable elders

Indicator	Indicator number	Description
Preventive advice	1	*All* vulnerable elders at an initial primary care visit should be counselled about intake of calcium and vitamin D and weightbearing exercises
Screening dual x-ray absorptiometry (DXA) scan for women	2	*All* female vulnerable elders without a diagnosis of osteoporosis should have documentation that they were offered a DXA scan
Screening DXA scan for men	3	*If* a male vulnerable elder without a diagnosis of osteoporosis has any of the following risk factors for osteoporosis: >3 months of systemic glucocorticoid treatment; primary hyperparathyroidism; osteoporosis in a first-degree relative; hypogonadism; gonadotropin-releasing hormone antagonist use; osteopenia on X-ray *Then* a DXA scan should be performed
Osteoporosis consideration after fracture	4	*If* a female vulnerable elder has a new non-pathological fracture, *then* she should be treated for osteoporosis, or a DXA scan should be performed
	5	*If* a vulnerable elder has a new hip fracture or undergoes kyphoplasty or vertebroplasty *then* a DXA scan should be performed or pharmacological therapy for osteoporosis should be prescribed within 6 months
Osteoporosis	6	*If* a vulnerable elder without osteoporosis is taking 7.5mg/d or more

Indicator	Indicator number	Description
prophylaxis for corticosteroids		of prednisone (or equivalent) for 1 month or longer, *then* he or she should be prescribed calcium and vitamin D supplements
	7	*If* a vulnerable elder without osteoporosis is taking 7.5mg/day or more of prednisone (or equivalent) for 3 months or longer, *then* he or she should be prescribed bisphosphonate therapy
Identifying secondary osteoporosis	8	*If* a female vulnerable elder is newly diagnosed with osteoporosis, *then* she should receive a workup including the following: medication use; alcohol use; complete blood count; liver function tests; renal function; calcium; phosphorus; vitamin D 25-OH; thyroid-stimulating hormone
Exercise for osteoporosis	9	*If* an ambulatory vulnerable elder has a new diagnosis of osteoporosis, *then* there should be documentation of advice to exercise within 3 months
Calcium and vitamin D for osteoporosis	10	*If* a vulnerable elder has osteoporosis, *then* he or she should be prescribed calcium and vitamin D supplements
Pharmacological treatment for female osteoporosis	11	*If* a female vulnerable elder has osteoporosis, *then* she should be treated with bisphosphonates, raloxifene, calcitonin, HRT or teriparatide (if this is a new diagnosis, within 3 months)
Testosterone for male osteoporosis	12	*If* a male vulnerable elder has osteoporosis and is hypogonadal, and has no history of prostate cancer, *then* he should be prescribed testosterone therapy
Pharmacological treatment for male osteoporosis	13	*If* a male vulnerable elder has osteoporosis, *then* he should be treated with bisphosphonates, calcitonin, parathyroid hormone or, if hypogonadal, testosterone (if this is a new diagnosis, within 3 months)

SOURCE: Assessing Care of Vulnerable Elders-3 Quality Indicators (2007)[150]

The ACOVE indicator set also includes a number of related osteoporosis quality indicators, as for example 'screen for falls' ('*all* vulnerable elders should have documentation that they were asked annually about the occurrence of recent falls') or 'tobacco counselling' ('*if* a vulnerable elder is ready to quit using tobacco, *then* there should be documentation of a quit date, discussion of therapies to aid cessation, and a follow-up visit within 1 month of the quit date').[150]

The ACOVE indicators have been proposed for use at health system or health plan level, as a means to identify areas in need of improvement. Application of these indicators to assess the quality of care provided to older patients living in the community in California found the care to be suboptimal, including for osteoporosis, with only 39 percent of women with newly diagnosed osteoporosis having been prescribed medication for the treatment within three months.[151] Similar application to nursing homes found treatment rates to be lower, at 20 percent.[152]

In addition to the ACOVE indicators, there are a number of typically national-level organisations that have developed, which are serving as a focal point for the endorsement of evidence-based quality measures, or provide a reference base for them. These include the National Committee for Quality Assurance (NCQA),[153] the National Quality Forum (NQF)[154] described earlier, and the National Quality Measures Clearinghouse (NQMC) of the US Agency for Healthcare Research and Quality (AHRQ).[155] Other national-level initiatives include the Physician Consortium for Performance Improvement® (PCPI™) of the American Medical Association (AMA).[156]

The NQMC provides a public repository for evidence-based quality measures and sets of measures developed elsewhere that meet the NQMC criteria for inclusion in the database; they include measures developed by the NCQF and endorsed by the NQF. Table 4.2 provides an overview of eight of the ten osteoporosis quality measures represented in NQMC, their sources and principal use (two indicators that relate to rheumatoid arthritis co-morbidity are not listed here).[157]

Table 4.2 Quality measures for osteoporosis represented in the National Quality Measures Clearinghouse

Quality measure	Source	Current use
Osteoporosis management in women who had a fracture: percentage of women aged 67 years and older who suffered a fracture, and who had either a BMD test or prescription for a drug to treat or prevent osteoporosis in the six months after the fracture	National Committee for Quality Assurance (NCQA)–Healthcare Effectiveness Data and Information Set (HEDIS)	Accreditation External oversight or Medicare Internal quality improvement
Osteoporosis testing in older women: the percentage of female Medicare members aged 65 and older who report ever having received a bone density test to check for osteoporosis	NCQA–HEDIS	Accreditation External oversight or Medicare Internal quality improvement
Percentage of female patients aged 65 years and older who have had a central DXA measurement ordered or performed at least once since age 60 or pharmacologic therapy prescribed within 12 months	Physician Consortium for Performance Improvement (PCPI)	Internal quality improvement National reporting
Percentage of patients aged 18 years and older with one of the following conditions or therapies: receiving oral glucocorticosteroid therapy for more than 3 months *or* hypogonadism *or* fracture history *or* transplant history *or* obesity surgery *or* malabsorption disease, *or* patients receiving aromatase therapy for breast cancer who had a central dual-energy X-ray absorptiometry (DXA) ordered or performed or pharmacologic therapy prescribed within 12 months	PCPI	Internal quality improvement
Percentage of patients aged 50 years and older treated for a hip, spine or distal radial fracture with documentation of communication with the physician managing the patient's ongoing care that a fracture occurred and that the patient was or should be tested or treated for osteoporosis	PCPI	Internal quality improvement National reporting
Percentage of patients aged 50 years and older with a diagnosis of osteoporosis who were prescribed pharmacologic therapy within 12 months	PCPI	Internal quality improvement National reporting
Percentage of patients aged 50 years and older with a fracture of the hip, spine or distal radius who had a central DXA measurement ordered or performed or pharmacologic therapy prescribed	PCPI	Internal quality improvement National reporting
Percentage of patients, regardless of age, with a diagnosis of osteoporosis who either received calcium and vitamin D or had documented counselling regarding calcium and vitamin D intake, and exercise at least once within 12 months	PCPI	Internal quality improvement

SOURCE: National Quality Measures Clearinghouse (2011)[157]

Two measures listed in Table 4.2 are part of the NCQA Healthcare Effectiveness Data and Information Set (HEDIS). HEDIS is a tool used by more than 90 percent of health plans

in the United States to measure performance on key dimensions of care and services.[158] Progress on these indicators is reported nationally in the annual State of Health Care Quality report published by the NCQA although presently covering health plans for Medicare patients only.[159]

4.3 Considerations for the development of quality indicators for the management of osteoporosis in Europe

In the introduction to this chapter we noted how there is a considerable need for the better understanding of current approaches and practices to managing postmenopausal osteoporosis in European settings to enable identified care gaps in the management of this condition to be addressed and so improve the overall quality of care for those with osteoporosis and associated fractures. The systematic use of quality indicators can provide a means to enable care quality to be tracked and the preceding section has provided a summary overview of quality indicators for the care of osteoporosis in current use in the United States. This section discusses the context for measuring the quality of osteoporosis care in European settings. In particular, it highlights some of the practical issues that need to be considered for the development and implementation of such indicators.

At the outset it is important to note that any indicator development will need to take account of context. In Section 4.1 we noted how indicator selection should be based on a set of core criteria, including importance, scientific acceptability, feasibility and usability. However, these criteria do not work like an 'algorithm' that will select an undisputed set of indicators based on explicit rules.[51] Indeed, in many instances, those who select indicators will need to judge whether or not a given measure meets a criterion, and such decisions will be context dependent. For example, priorities differ between healthcare systems, so the 'importance' criterion is likely to be judged differently across different systems; in the case of postmenopausal osteoporosis different emphases might be placed on the prevention, diagnosis or treatment of the condition.

Similarly, evaluation of the 'scientific acceptability' criterion has to incorporate expert opinion as only a few areas of medicine, for example coronary heart disease, can build on an evidence base robust enough to be used as the sole source of information.[131 138] This point may pose a particular challenge in relation to the transferability of quality indicators between countries,[160] because of differences in professional opinion and in the interpretation of evidence; also the evidence base used might vary, for example building on evidence that is available in the native language of one country only.[161-163] The second-last point is likely to be of relevance for the selection of indicators for the use of fracture risk tools, with expert opinion of the usefulness of for example the FRAX® tool divided, as reflected in guidelines in place in different European countries.[66-67 69 72 110]

Overall, structured expert consultation methods, such as the RAND/UCLA Appropriateness Method, can and have been widely used as formal and transparent methods of combining evidence with professional opinion in order to develop quality indicators.[164] An adaptation of this method was employed by Steel et al. (2004) to assess transferability of the US Assessing Care of Vulnerable Elders project[147] described in the preceding section to the English context.[162] Following this process, 102 quality indicators were rated as valid for use in England, of which 32 were piloted in the English longitudinal

study of ageing. These also considered two of the ACOVE osteoporosis indicators: (a) '*If* a person aged 50 or older has untreated osteoporosis, *then* calcium and vitamin D supplements should be recommended at least once'; (b) '*If* a woman aged 50 or older is newly diagnosed with osteoporosis, *then* the patient should be offered treatment with hormone replacement therapy, SERMs, bisphosphonates, calcitonin, or calcium and vitamin D within 3 months of diagnosis'.[90]

In our review of current approaches and practices to managing postmenopausal osteoporosis by means of country case studies of England, France, Germany and Spain presented in Chapter 3 of this report, we also considered information provided by country key informants to help understand system features in relation to osteoporosis. In this context, we invited key informants to provide a list of up to five quality indicators they considered suitable for the monitoring and assessment of the management of osteoporosis or osteoporosis-related fractures among postmenopausal women.

Table 4.3 presents quality indicators proposed by three key informants in England, France and Germany, grouped according to principal domains. Given the small number of key informants, this list should be interpreted as indicative only. However, it is notable that all informants listed indicators to enable tracking the size of the osteoporosis burden, risk assessment and diagnosis as well as treatment rates as highly relevant. It may be also worth noting that the proposed indicator 'Number of DXA measurements performed' was interpreted as 'a good marker where uptake is low' (France) while at the same time only considered useful if related to age to measure appropriate use (Germany).

Table 4.3 Quality indicators for the monitoring and assessment of the management of osteoporosis or osteoporosis-related fractures among postmenopausal women proposed by three country key informants

Domain	Potential indicator(s) (key informant country)
Understanding the burden of osteoporosis and associated fractures	Primary indicator: • number or incidence of hip fractures (England, France) • documentation of falls (register) (Germany) Secondary indicator: • incidence of second fractures (England) • number of fractures other than of hip (France)
Prevention	Number of vitamin D prescriptions (France)
Risk assessment or diagnosis	Use of risk assessment including FRAX and bone densitometry at ages 50–75 years (England) Number of DXA measurements performed (France, Germany)
Treatment	Market size for osteoporotic medications (France) Prescription of osteoporotic medication by age group (Germany) Therapeutic intervention for all women following low trauma fracture after age 50 years (England) Number of women with fractures receiving prescription osteoporosis drugs (Germany)

Given the small sample size, we do not intend to interpret the proposed indicators presented in Table 4.3 further but suggest that these should form a starting point for the

further development of quality measures for postmenopausal osteoporosis in Europe. Such development might be able to draw, to a considerable extent, on experiences in the United States, where a small set of indicators related to the testing and management of osteoporosis in women is already being used routinely to monitor the quality of care provided to Medicare patients.[159] These are (Table 4.2):

- osteoporosis management in women who had a fracture: percentage of women 67 years of age and older who suffered a fracture, and who had either a BMD test or prescription for a drug to treat or prevent osteoporosis in the six months after the fracture
- osteoporosis testing in older women: the percentage of female Medicare members 65 years of age and over who report ever having received a bone density test to check for osteoporosis

In addition, the routine measurement of the management of postmenopausal osteoporosis in primary care is currently under consideration for inclusion in the Quality and Outcomes Framework as part of the GP contract in the UK (see Section 3.2).[82] Measures are:

- the practice can produce a register of patients (i) aged 50–74 years with a record of a fragility fracture and a diagnosis of osteoporosis confirmed on DXA scan, and (ii) aged 75 years and over with a record of a fragility fracture
- the percentage of patients aged between 50 and 74 years, with a fragility fracture, in whom osteoporosis is confirmed on a DX scan, who are currently treated with an appropriate bone-sparing agent

the percentage of patients aged 75 years and over with a fragility fracture, who are currently treated with an appropriate bone-sparing agent It is however important to note that the implementation of quality measures will crucially depend on the actual availability of data, which are likely to vary across European healthcare systems. While routinely collected data such as claims data will be available, and are increasingly being used for quality measurement,[145] such data can be problematic as they tend to lack the level of clinical detail required to assess many aspects of quality. These challenges are illustrated in several US studies, aiming to adapt indicators developed within the Assessing Care of Vulnerable Elders project for use with routinely collected data, finding this to be feasible for a proportion of indicators only.[151-152] [165] For example, one study found that of 182 quality indicators covering 22 conditions, only 37 could be constructed from administrative data.[165] This was the case for three out of six indicators for osteoporosis. Importantly, the overall performance was 70 percent on the three indicators derived from administrative data, but only 46 percent on those that were based on a medical record. This implies that using administrative data as the sole source to assess quality might overestimate performance. However, indicator performance will depend, to a considerable extent, on the nature of the indicator to be assessed. For example, a recent Canadian study examined applicability of the two osteoporosis quality measures used by the NCQA and HEDIS to monitor care for Medicare patients described above to administrative data (medical and pharmacy claims data) in Canada.[166] The analysis found that healthcare utilisation data may provide an adequate means to assess the quality of osteoporosis management in routine practice, but highlighted that such data are not sufficient for identifying women with underlying osteoporosis.

The UK is one of the few countries that has designed its national electronic medical record systems specifically to assess quality of care as part of its pay for performance scheme. While this is a considerable step forward in providing information on quality of care, the requirement routinely to code clinical information brings its own problems, such as the need to train doctors, to lengthen consultations to record data, the risk of gaming or fraud, and so on.[51] However, such a system will provide a means to allow the routine monitoring systems to enable better understanding of contemporary patterns and trends and identify care gaps in the management of this condition. Such analyses are crucial to inform targeted strategies and policies to address effectively the burden of osteoporosis and associated fractures, which is sizable and set to increase across Europe.

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APPENDICES

Appendix A: Overview of guidelines in place in four countries

Table A1. Main features of national guidelines for the management of postmenopausal osteoporosis in England, France, Germany and Spain

Title	Organisation	Year issued (last update)	Frequency of updates	Goal	Scope	Target group
England/UK						
Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)[66]	National Institute for Health and Clinical Excellence (NICE)	2008 (2011)	Not stated	To provide guidance related only to treatments for the primary prevention of fragility fractures in postmenopausal osteoporotic women	Postmenopausal women who have osteoporosis (defined by T-score =/< −2.5 SD). It is assumed that women being treated have an adequate calcium intake and are vitamin D replete.	Healthcare professionals (clinicians)
Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)[67]	NICE	2008 (2011)	Not stated	To provide guidance related only to treatments for the secondary prevention of fragility fractures in postmenopausal osteoporotic women who sustained a fragility fracture	Postmenopausal women who have osteoporosis (defined by T-score =/< −2.5 SD) and have sustained a clinically apparent osteoporotic fragility fracture. It is assumed that women receiving treatment have an adequate calcium intake and are vitamin D replete.	Healthcare professionals (clinicians)
Denosumab for the prevention of osteoporotic fractures in postmenopausal women[69]	NICE	2010	Not stated	Not stated	Postmenopausal women at increased risk of fractures who are unable to comply with administering instructions for alendronate and either risedronate or etidronate; or have an intolerance or contraindication to those treatments. For	Healthcare professionals (clinicians)

Title	Organisation	Year issued (last update)	Frequency of updates	Goal	Scope	Target group
					primary prevention, they must also have a specified combination of T-score, age and number of independent clinical risk factors for fracture.	
Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men aged 50+ in the UK[72]	National Osteoporosis Guideline Group (NOGG)	2008 (2010)	5 years (max)	To provide a clinical guideline for the management of men and women at high fracture risk To update earlier Royal College of Physicians' guidelines in light of appraisals by NICE and development of a fracture risk assessment tool (FRAX®)	Postmenopausal women and men aged 50+	Not made explicit
France						
Traitement medicamenteux de l'ostéoporose post-monopausique[102] *(Medical treatment of postmenopausal osteoporosis)*	Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps)	2006 (2008)	Not stated	To provide a best practice guide for the treatment and prevention of postmenopausal osteoporosis To prevent fractures in a 5 to 10-year span	Postmenopausal women	Not made explicit – clinicians diagnosing and treating osteoporosis
Prevention, diagnostic et traitement de l'ostéoporose – note de synthèse[101] *(Prevention, diagnostic and treatment of osteoporosis – synthesis note)*	Haute Authorité de Santé (HAS)	2006	Not stated	Response to one of the priorities identified by the Ministry of Health in 2005 and to the referral of the General Director of the National Union of Health Insurance (Union nationale des caisses d'assurance maladie) on the reimbursement of the prevention, diagnosis and drug treatment of osteoporosis including the precise definition of when densitometry is advised	Prevention, diagnosis and treatment of osteoporosis generally	Not stated
Germany						
DVO Leitlinie 2009 zur Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen[110] *(DVO Guideline 2009 for the prevention, diagnosis and therapy of osteoporosis in adults)*	Dachverband Osteologie eV (DVO)	2003 (2009)	3 years	To optimise care processes, to minimise the incidence of fracture, and to enhance quality of life and functioning of patients with fractures	Primary and secondary osteoporosis among adults	Primary care physicians and specialists with special interest in osteoporosis; allied health professionals involved in the diagnosis and treatment of osteoporosis

Title	Organisation	Year issued (last update)	Frequency of updates	Goal	Scope	Target group
Spain						
Guías de práctica clínica en la osteoporosis posmenopáusica, glucocorticoidea y del varón[123] *(Clinical practice guidelines for postmenopausal, steroid and male osteoporosis)*	Sociedad Española de Investigacion Ósea y del Metabolismo Mineral (SEIOMM)	2001 (2008)	Previous update was after 5 years	Harmonise treatment, provide recommendations for the establishment of protocols and assist clinical practice	Post-menopausal osteoporosis, steroid-induced osteoporosis and osteoporosis in men	Primary care clinicians and specialised clinicians involved in the medical treatment of osteoporosis

Table A2. Main features of national guidelines for the management of postmenopausal osteoporosis in England, France, Germany and Spain - *continued*

Title	Recommended preventative measures	Risk assessment	Use of FRAX®	Principal diagnostic examination
England/UK				
Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)	No recommendations concerning population-based strategies for prevention (increasing physical activity at all ages, reducing smoking prevalence). Recommended prevention: alendronate (for three specific groups of women); risedronate and etidronate as alternative options in specific cases where alendronate cannot be taken; strontium ranelate (only when other treatments cannot be taken). Raloxifene is not recommended.	Low BMD=BMI < 22kg/m2, medical conditions (ankylosing spondylitis, Crohn's disease, prolonged immobility-related) and untreated premature menopause *or* Independent clinical risk factors: parental history of hip fracture, alcohol intake of 4 or more units/day and rheumatoid arthritis	Fracture risks derived from FRAX were entered into the economic models of the assessment group. However, the Committee did not support recommendations about treatment based on absolute risk calculated by FRAX for 3 reasons (not all clinical risk factors included in the WHO algorithm are appropriate; absolute fracture risk is not directly related to cost-effectiveness; treatment benefit not proved for fracture risk associated with all independent clinical risk factors).	A combination of T-score, age and number of independent clinical risk factors for fracture
Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)	No recommendations concerning population-based strategies for prevention (increasing physical activity at all ages, reducing smoking prevalence). Recommended prevention: Alendronate; risedronate and etidronate as alternative options in specific cases where alendronate cannot be taken; strontium ranelate and raloxifene (only when other treatments cannot be taken); and teriparatide as an alternative when no other treatments can be used and patient has T-score =/< 4 plus two fractures.	Independent clinical risk factors: - parental history of hip fracture - alcohol intake of 4 or more units/day - rheumatoid arthritis	Fracture risks derived from FRAX were entered into the economic models of the Assessment Group. Committee did not support recommendations about treatment based on absolute risk calculated by FRAX for 3 reasons (not all clinical risk factors included in the WHO algorithm are appropriate; absolute fracture risk is not directly related to cost-effectiveness; treatment benefit not proved for fracture risk associated with all independent clinical risk factors).	A combination of T-score, age and number of independent clinical risk factors for fracture
Denosumab for the prevention of osteoporotic fractures in postmenopausal women	Treatment with Denosumab for primary and secondary prevention only in women at increased fracture risk who cannot be treated with the recommended drugs.	Independent clinical risk factors: - parental history of hip fracture - alcohol intake of 4 or more units/day - rheumatoid arthritis	FRAX used in subgroup analysis by manufacturer. The committee was mindful that the tool was unvalidated at the time.	A combination of T-score, age and number of independent clinical risk factors for fracture
Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK	No recommendations concerning population-based strategies for prevention (increasing physical activity at all ages, reducing smoking prevalence and increasing dietary calcium intake).	BMD, plus risk factors (age; sex; low body mass index; previous fracture; parental history of hip fracture; current glucocorticoid treatment; current smoking; alcohol intake of 3 or more units	Yes. 'In the presence of other clinical risk factors, the ten-year probability of a major osteoporotic fracture should be determined using FRAX®).'	History and physical examination Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase

Title	Recommended preventative measures	Risk assessment	Use of FRAX®	Principal diagnostic examination
	Recommended prevention: Selective case finding; supplementation of 800 IU vitamin D and 1–1.2g calcium daily for housebound elderly and those in residential care homes; alendronate (5mg daily); raloxifene (60mg daily); etidronate (90-day cycles, 400mg first 14 days); HRT (restricted to younger postmenopausal women)	daily; secondary causes of osteoporosis; falls). Other procedures (if indicated)	'In men and women who require a BMD test, fracture probabilities should be recomputed with FRAX®. Treatment can be considered in those in whom fracture probabilities lie above the intervention threshold.'	and liver transaminases Thyroid function tests Bone densitometry (DXA)
France				
Medical treatment of postmenopausal osteoporosis	Treatments described are only proposed to be applied after correction of a possible calcium and/or vitamin D deficiency through diet or supplements	The following are risk factors to consider: - age - fracture due to frailty - densitometry - associated risks such as current or previous corticotherapy, family history of femur fracture in parents, degenerating eye sight, low BMI, neuromuscular or orthopaedic disorders, smoking	Not mentioned	Medical history Osteodensitometry where: - history of vertebral fracture or femur without major trauma in parents (1st degree) - BMI >19kg/m2 - onset of the menopause before 40 years or iatrogenic menopause - history of prolonged corticotherapy (more than 3 months) with corticoide dose equal to 7.5mg per day
Prevention, diagnostic and treatment of osteoporosis – synthesis note	Physical activity; calcium and vitamin D intake; smoking cessation; reduction in alcohol intake; maintenance of normal weight and BMI; fall prevention HRT for the treatment of climacteric symptoms that impact on quality of life at minimum effective dose and for the shortest duration possible with regular re-evaluation of risks and benefits. Also used for women at high risk of fracture in case of intolerance or contra-indication of other treatments advised for osteoporosis. Bisphosphonates and raloxifen: alendronate (5mg), ibandronate (2.5mg), risedronate (5mg) and raloxifen for the prevention of osteoporosis in postmenopausal women at		Not mentioned	Patient history, clinical assessment of risk factors for osteoporosis or its complications. Only after the above factors have been assessed should a densitometry be requested. Densitometry is only indicated if its results could lead to a therapeutic modification of the patients' care pathway.

Title	Recommended preventative measures	Risk assessment	Use of FRAX®	Principal diagnostic examination
	high risk of osteoporosis. However, the CT (Commission de la Transparence) has not approved these for reimbursement in its notification on 5 July 2006.			
Germany				
DVO Guideline 2009 for the prevention, diagnosis and therapy of osteoporosis in adults	Defined as 'all general measures which lead, or may lead to an improvement in bone stability and/or a reduction in fall-associated peripheral fractures in all areas of primary to tertiary prevention' Muscle strength, coordination and falls through regular physical exercise; annual assessment of falls history for those aged 70+; vitamin D intake to reduce risk of falls Diet and lifestyle: diet supplementation with vitamin D plus calcium (calcium on its own recommended when dietary calcium under 1000g/d); sustain sufficient caloric intake to avoid low weight; avoid smoking	Age and sex dependent; clinical profile with a 20% or higher 10-year risk for vertebral and/or hip fracture as cut-off for diagnostic investigation Previous fracture(s); level of comorbidity and medication; for women aged 70+ and men aged 80+ actual age generally viewed as cut-off for diagnostic investigation	No: FRAX still under development with further changes expected; also DVO risk assessment considered to better reflect actual fracture risk than FRAX	Medical history, clinical examination, DXA bone mineral density measurement plus laboratory tests and imaging to identify prevalent vertebral fractures where appropriate
Spain				
Clinical practice guidelines for postmenopausal, steroid and male osteoporosis	General health advice including increasing physical activity, smoking cessation, increase in calcium intake and vitamin D Fall prevention is particularly important. Elderly people should be given specific advice to avoid falls.	BMD, plus age, previous fracture and clinical risk factors	Not mentioned	Clinical assessment combined with bone densitometry to assess likelihood of fracture risk Use of DXA measurement and considered more effective than conventional x-rays; use of x-rays recommended in selected cases Bone markers mentioned as complementary diagnostic tool for assessing fracture risk

Table A3. Main features of national guidelines for the management of postmenopausal osteoporosis in England, France, Germany and Spain - *continued*

Title	Criteria for pharmaceutical treatment	Recommended drugs	Other drugs
England/UK			
Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)	Women with confirmed osteoporosis who: - are aged 75+ - are aged 70+ with an independent clinical risk factor for fracture or an indicator of low BMD - are aged 65–69 with an independent clinical risk factor for fracture - are postmenopausal under 65 years with an independent clinical risk factor for fracture and at least one additional indicator for low BMD	Alendronate Risedronate or etidronate Strontium ranelate	n/a
Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)	Women with confirmed osteoporosis who: - are aged 75+ - are aged 70+ with an osteoporotic fracture - are aged 65+ with T-score =/< −4 SD, or T-score =/< −3.5 plus >2 fractures (teriparatide) - are aged 55–64 with T-score =/< −4SD plus >2 fractures (teriparatide)	Alendronate Risedronte or etidronate Strontium ranelate Raloxifene Teriparatide	n/a
Denosumab for the prevention of osteoporotic fractures in postmenopausal women	Primary prevention: postmenopausal osteoporotic women at increased risk of fracture who cannot administer or tolerate alendronate and either risedronate or etidronate *and* who have a specified combination of T-score, age and number of independent clinical risk factors (RFs) for fracture 0 clinical RF: 70–74 years: −4.5 SD (T-score) 75+: −4.0 SD (T-score) 1 clinical RF: 65–69: −4.5 SD (T-score) 70–74: −4.0 SD (T-score) 75+: −4.0 SD (T-score)	Alendronate Risedronate or etidronate Denosumab	n/a

Title	Criteria for pharmaceutical treatment	Recommended drugs	Other drugs
	2 clinical RFs: 65–69: −4.0 SD (T-score) 70–74: −3.5 SD (T-score) 75+: −3.0 SD (T-score) For secondary prevention: only in women at increased fracture risk who cannot administer or tolerate alendronate and either risedronate or etidronate		
Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men aged 50+ in the UK	Women with prior fragility fracture FRAX® thresholds for intervention: - 7.5% at 50 years - 10% at 55 years - 12.5% at 60 years - 15% at 65 years - 20% at 70 years - 25% at 75 years - 30% at 80 years	Alendronate Ibandronate Risedronate Zoledronate Denosumab Strontium ranelate Raloxifene Teriparatide (PTH 1-34) Recombinant human PTH (1-84)	Calcitonin Calcitriol Etidronate HRT (restricted to younger postmenopausal women)
France			
Medical treatment of postmenopausal osteoporosis	Recommendations for post-menopausal women: For those women who have had a fracture: - osteoporosis as ascertained through densitometry: pharmaceutical treatment is recommended - osteopenia as ascertained through densitometry: pharmaceutical treatment should not be systematic (unless fracture of vertebra or fracture of proximal femur) For those women who have not had a fracture: - osteoporosis: treatment can be discussed before 60 years of age. Treatment must be discussed between 60 and 80 years of age - osteopenia: treatment is not recommended (unless important	Alendronate Risedronate Raloxifene Teripatide Stronitum ranelate	

Title	Criteria for pharmaceutical treatment	Recommended drugs	Other drugs
	associated risk factors are present)		
Prevention, diagnostic and treatment of osteoporosis – synthesis note	Case by case evaluation of fracture risk (including bone mineral density and other risk factors). Tests for calcium and/or vitamin D deficiency are essential before the start of treatment and supplements must be prescribed in cases of deficiency When a patient presents with a fragility fracture (or a history of such fractures) and where densitometry has established a T-score equal or below −2.5 treatment is necessary. For women at risk of osteoporosis but without a fracture, alendronate, risedronate, raloxifene and strontium ranelate are indicated to reduce the risk of vertebral and/or hip fractures but these are not currently reimbursed without presence of osteoporosis-related fracture.	When a patient presents a fragility fracture (or a history of such fractures) and that densitometry has established a T-score equal or below −2.5, treatment is necessary. Recommended drugs are: - bisphosphonates (alendronate 10 and 70mg; risedronate 5 and 35mg; etidronate 400mg – limited use because evidence of effectiveness below that for alendronate and risedronate) - raloxifen: preferably for patients at low risk of non vertebral fracture (neck of the femur) - strontium ranelate: reduces risk of both vertebral and hip fractures - teripatide: reserved for the treatment of acute osteoporosis with at least 2 vertebral fractures - for postmenopausal osteoporosis All these drugs are reimbursed.	Ibandronate – not yet commercially available in France, effectiveness only evidenced on vertebral fractures
Germany			
DVO Guideline 2009 for the prevention, diagnosis and therapy of osteoporosis in adults	Estimated 10-year risk of vertebral and hip fracture > 30 % and reduced T-score as assessed by DXA measurement at lumbar spine, total hip or femoral neck (lowest value) of <-2.0 Without fracture or other specific risk factures DXA-T-value; age and sex specific: <−2.0 for women >75 and men >85 <−2.5: 70–75 and 80–85 <−3.0: 65–70 and 75–80 <−3.5: 60–65 and 70–75 <−4.0: 50–60 and 60–70	To reduce fractures in postmenopausal women: - alendronate - ibandronate - teriparatide - oestrogen - PTH - raloxifen - risedronate - strontium ranelate - zoledronate	Recommended only where intolerance of A-rated drugs or because of patient preferences as strength of evidence of effectiveness in reducing fractures lower: - alfacalcidol - calcitonin - etidronat - fluoride - nandrolone-decanoate
Spain			

Title	Criteria for pharmaceutical treatment	Recommended drugs	Other drugs
Clinical practice guidelines for postmenopausal, steroid and male osteoporosis	For all patients with postmenopausal osteoporosis, guarantee adequate intake of vitamin D and calcium For patients at high risk of fractures (more than 2 vertebral fractures): PTH 1-34 (alternative is standard treatment: alendronate and risedronate) For patients at age over 65 years and at minor risk of hip fracture: raloxifen (alternative is standard treatment: alendronate and risedronate) For patients who do not fall within above categories: standard treatment alendronate and risedronate. If inadequate response to standard treatment: PTH 1-34. If other preference or side-effects with standard treatment: strontium, ibandronate, raloxifen, etidronate or calcitonin	Strontium Ibandronate Raloxifen Etidronate Calcitonin Alendronate Risedronate Parathyroid hormone (PTH 1-34)	Other drugs mentioned in the guidelines where evidence of treatment or prevention effectiveness is more limited or mixed include: - thiazide - ostrogen therapy - tibolone - isoflavone - bisfosfonates - zoledronate - denosumab

Table A4. Main features of national guidelines for the management of postmenopausal osteoporosis in England, France, Germany and Spain - *continued*

Title	Monitoring: patients with moderate fracture risk	Monitoring: patients undergoing pharmaceutical treatment	Duration of treatment
England/UK			
Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)		Optimal duration of treatment with individual bisphosphonates requires further research Teriparatide restricted to 18 months by marketing authorisation	
Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)		Optimal duration of treatment with individual bisphosphonates requires further research Teriparatide restricted to 18 months by marketing authorisation	
Denosumab for the prevention of osteoporotic fractures in postmenopausal women		Model assumed 5 years – considered to reflect clinical practice	
Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK	Unclear	Repeated estimations of BMD and markers of bone formation and/or bone resorption	Unclear
France			
Medical treatment of postmenopausal osteoporosis	Post-menopausal women with osteopenia on its own do not require treatment, however, if accompanied by fractures resulting from low energy trauma, it can warrant discussion of treatment. If T score is −2.5<T<=−1 (osteopenia), treatment is not recommended as risk of fracture is low. Outcome can be re-assessed with another bone density scan after 3 to 5 years. If then T<=−2 and other fracture risks are present then treatment can be advised.	Bone density measurement not recommended for monitoring of patients under treatment although bone density measurement is recommended for prescription of treatment. Second bone density measurement recommended at the end of treatment (except in cases where treatment is stopped because of side-effects) and measurement should be taken into account when re-evaluating risk of fracture In some cases (anti-resorptive treatment), bone remodelling marking can enable assessment of treatment effectiveness on bones Other ways to monitor treatment are: - to monitor height - to take a standard x-ray	Treatment duration will depend on: - fracture risk – treatment duration will increase with initial risk - clinical effectiveness of treatment (fracture within 1st year of treatment=treatment failure) - available data on treatment impact on bones and treatment tolerance for post-menopausal women with osteoporosis
Prevention, diagnostic and treatment	A second densitometry can be carried out in	A second densitometry is recommended when anti-osteoporotic	Treatment with bisphosphonates, raloxifen

Title	Monitoring: patients with moderate fracture risk	Monitoring: patients undergoing pharmaceutical treatment	Duration of treatment
of osteoporosis – synthesis note	cases where treatment has not been given following a first densitometry showing a normal value or osteopenia. In those cases, a second densitometry can be carried out 3 to 5 years later if additional risk factors have been identified.	treatment is stopped unless treatment is stopped early because of side-effects It is not recommended to check on treatment effectiveness or treatment compliance. During treatment, if a fracture occurs after the first year and the patient has been following the treatment indicated, the treatment must be stopped and replaced with another drug. After 1 year, the decision to continue the treatment (or in cases of treatment with teriparatide, the decision to start the patient on another drug such as a bisphosphonate) rests on the re-evaluation of individual risks of fracture.	or strontium ranelate must be of at least 4 years. Treatment with teriparatide must last 18 months maximum.
Germany			
DVO Guideline 2009 for the prevention, diagnosis and therapy of osteoporosis in adults	2-yearly re-evaluation of fracture risk recommended; for those taking glucocorticoids 6–12 months); DXA measurement within 2–5 years	Initial follow-up 3–6 months; subsequently 6–12 months Comprehensive re-evaluation incl. DXA recommended after 2 years In absence of clear criteria for therapy failure change of medication regime only recommended in cases of evidence of loss of BMD or occurrence of 2–3 fractures within 3 years	Typically long term because of chronicity of osteoporosis Pharmaceutical treatment may be terminated where significant risk factors disappear (e.g. smoking, falls, improved mobility); however, re-evaluation of fracture risk is recommended after 1–2 years
Spain			
Clinical practice guidelines for postmenopausal, steroid and male osteoporosis	Unclear but states monitoring intervals advised for patients without treatment should be more than every 2 years	Densitometry monitoring is advised to assess treatment effectiveness and to identify patients who are non-responsive to treatment. DXA of central skeletal sites is advised for monitoring osteoporosis in diagnosed patients; guidelines state that DXA of peripheral skeletal sites are not appropriate for monitoring or diagnosis of osteoporosis. Bone markers (e.g. alcalin phosphate; pyridinoline, etc) are mentioned as a complementary diagnosis tool for assessing fracture risk and response to treatment. Monitoring interval must be based on the condition of the patient and taking into account that the change expected (in bone density) must be equal or exceed the minimum significant change that is detectable by the diagnosis method. Monitoring intervals are advised as follows: - for patients without treatment: more than every 2 years - for patients receiving osteoporosis treatment: first control or check	Treatment with teriparatide to be followed at 18 months with an anti-resorptive (treatment with this drug is limited to 18 months) Some evidence from studies on treatment length for individual drugs but no formal recommendation

Title	Monitoring: patients with moderate fracture risk	Monitoring: patients undergoing pharmaceutical treatment	Duration of treatment
		up within 1 to 2 years followed by intervals of 2 years - in exceptional circumstances (e.g. transplants): between 6 and 12 months	

Appendix B: Interview topic guide

Postmenopausal osteoporosis management

- Interview topic guide -

1. **To what extent is there a national/overarching strategy in your country targeting osteoporosis?**

2. **To what extent is there a national guideline for the prevention, management and/or treatment of postmenopausal osteoporosis in your country?**

3. **What evidence is there on the extent of implementation of the national guideline for postmenopausal osteoporosis in practice?**

4. **What is the evidence on the uptake of preventive interventions for postmenopausal women with osteoporosis/osteoporosis-related fractures in your country?**

5. **What is the evidence on the uptake of therapeutic interventions for postmenopausal women with osteoporosis/osteoporosis-related fractures in your country?**

6. **Who typically diagnoses and/or treats a patient with osteoporosis? To what extent do you consider the current approach to the diagnosis and treatment of osteoporosis appropriate?**

7. **To what extent do current approaches to managing osteoporosis/osteoporosis-related fractures draw on new organisational approaches to care** (eg case management; structured disease management; risk stratification)**?**

8. **How would you rate the quality of care for postmenopausal women with osteoporosis/osteoporosis-related fractures in your country and why?** Please consider prevention, diagnosis and treatment.

9. **What would you consider are the main gaps/barriers towards achieving better management of postmenopausal women with osteoporosis/osteoporosis-related fractures in your country?**

10. Please list your <u>top-five indicators</u> for high quality care for the management of osteoporosis/osteoporosis-related fractures among postmenopausal women. Why would you select these?