EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

SCREENING FOR OSTEOPOROSIS IN THE GENERAL POPULATION

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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Conflict of interest

All authors, co-authors, dedicated reviewers, external experts, and patients involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator assessed according to the EUnetHTA Declaration of Interest and Confidentiality Undertaking of Interest (DOICU) form.

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LIST OF ABBREVIATIONS

ACP	American College of Physicians
AHRQ	Agency for Healthcare Research and Quality
AQuAS	Agency for Health Quality and Assessment of Catalonia
BMD	Bone mineral density
BMI	Body mass index
CE	Communauté européenne
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CUR	Health problem and current use of technology
CTXA	Computed tomography x-ray absorptiometry
CVF	Clinical vertebral fractures
DVO	Dachverband der Deutschsprachigen Wissenschaftlichen osteologischen Gesellschaften e.V. (umbrella organisation for German-speaking scientific societies on osteology)
DXA	Dual-energy x-ray absorptiometry
ED	Enrichment design
EFF	Effectiveness
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
EU	European Union
EUnetHTA	European network for Health Technology Assessment
EQ-5D	EuroQol 5-dimension scale
FRAX	Fracture risk assessment tool
GÖG	Health Austria (Gesundheit Österreich) GmbH
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GP	general practitioner
HR	Hazard ratio
HrQoL	Health-related quality of life
HTA	Health technology assessment
ICD	International classification of diseases
IOF	International osteoporosis foundation
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
IVA	Instant vertebral assessment

LBI-HTA	Ludwig-Boltzmann-Institute for Health Technology Assessment
MB-SD	Marker-based strategy design
MeSH	Medical Subject Headings
MOF	Major osteoporotic fractures
ND	No data
NICE	National Institute for Health and Care Excellence
NSPHMPDB	National School of Public Health, Management and Professional Development Bucharest
OCF	Other clinical fractures
ORF	Osteoporosis-related fractures
OPTOQoL	Osteoporosis-specific quality of life
OR	Odds ratio
ORAI	Osteoporosis risk assessment instrument
OSIRIS	Osteoporosis index of risk
OST	Osteoporosis self-assessment tool
PTH	Parathyroid hormone
RANK	Receptor activator of nuclear factor-κB
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RR	Relative risk
SAF	Safety
SCORE	Simple calculated osteoporosis risk estimation
SD	Standard deviation
SERM	Selective oestrogen-modulators
SF-12	Short form 12 health survey questionnaire
SF-36	Short form 36 health survey questionnaire
SHR	Sub-hazard ratio
SNHTA	Swiss Network for HTA
SR	Systematic review
TEC	Description and technical characteristics of technology
TBS	Trabecular bone score
UK	United Kingdom
USA	United States of America
USPTF	US Preventive Task Force

qCT	Quantitative computer-tomography
qUS	Quantitative ultrasound

SUMMARY OF RELATIVE EFFECTIVENESS OF SCREENING FOR OSTEOPOROSIS IN THE GENERAL POPULATION

Scope

The scope can be found here: see Scope.

Introduction

Description of technology and comparators

Patients with osteoporosis-related fracture risk can be identified either via organised screening or opportunistically by case finding [1]. However, there is currently no agreed policy for osteoporosis screening in Europe [1]. In the context of this Rapid Relative Effectiveness Assessment (REA), population-based screening using a clinical risk assessment tool and / or bone mineral density (BMD) measurement (dual-energy x-ray absorptiometry [DXA], quantitative ultrasound [qUS], or quantitative computer-tomography [qCT]) was evaluated and then compared with usual care, i.e. no screening. Various tools for assessing the risk of fracture or osteoporosis have been developed, as BMD measurement alone fails to identify many patients at risk of fracture [1-3]. These tools are used to make decisions regarding further diagnostic work-up of patients and / or to directly make a decision regarding their eligibility for treatment [1,2,4]. Risk factors include sex, age, body mass index (BMI), and lifestyle [1].

The aim of screening and the subsequent changes in drug and / or non-drug management is to avoid the significant morbidity and mortality associated with osteoporotic fractures.

Health problem

Osteoporosis is defined as “a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [5,6]. A report on osteoporosis in the European Union (EU) presented age-related prevalence rates for the 27 EU member states in the year 2010: the prevalence of osteoporosis increased from 6.3 % (women) and 2.5 % (men) in the age group of 50 to 54 years to 47.2 % (women) and 16.6 % (men) in the age group of 80 years or older [7]. Data from 2015 and 2017 for 6 EU countries showed that the estimated lifetime risk of major osteoporotic fractures in persons aged 50 was 18 % in men and 31 % in women (https://www.iofbonehealth.org/print/11862).

Osteoporosis screening would be performed in the general population (population-based screening). No age cut-off was pre-defined for the purpose of this Rapid REA, even though the prevalence of osteoporosis increases with age [8]. The current guideline of the US Preventive Services Task Force (USPSTF), for example, recommends screening in postmenopausal women aged 65 years and older and in postmenopausal women under 65 who have an increased risk of osteoporosis [8]. For men, the authors conclude that there is insufficient evidence on the benefits and harms of screening [8]. Besides general measures to reduce or eliminate risk factors for osteoporosis-related fractures and to reduce the risk of falls, a range of drugs has been developed for the treatment of osteoporosis, such as bisphosphonates and selective oestrogen receptor modulators (SERMs) [1,8-12].

Methods

The target population of the present assessment was the general population. The test intervention was screening for osteoporosis. The control intervention was no screening (i.e. usual care).

The following patient-relevant outcomes were considered:

- Symptomatic fractures (critical outcome)
- Mortality (overall and fracture-related)
- Health-related quality of life (HrQoL)
- Pain
- Body function and activities of daily living
- Use of resources (e.g. visits to doctors and hospitals, admission to nursing homes)
- (Serious) adverse events
- Overdiagnosis / overtreatment.

Only randomised controlled trials (RCTs) in 2 different designs were included in this Rapid REA. Marker-based strategy design RCTs ("strategy design RCTs") formed the main body of evidence. As long as they have no important limitations, these trials provide high quality evidence. A strategy design RCT is equivalent to a 'conventional' screening study, where participants are assigned to either screening (i.e. diagnostic test + treatment for test-positive persons) or no screening. Enrichment-design RCTs were used as additional evidence. In an enrichment design, patients are randomly assigned (only after a positive screening test) to a treatment or a control arm, so no comparative data are available for the test-negative persons. As enrichment design studies consequently evaluate only a part of the entire screening-treatment process, in this Rapid REA, the quality of evidence from these trials was downgraded by 2 levels due to indirectness. Participants should have been recruited from the general population, which should have been clearly described in the publications of these trials. Enrichment design studies were mainly included in this report because it was assumed that strategy design studies would not adequately report (serious) adverse effects of anti-osteoporosis treatment. For pragmatic reasons, only enrichment design studies limited to drug treatment were included, as it was assumed that the most important adverse effects (qualitative and quantitative) would result from this type of treatment [13]. Non-drug treatment options (e.g. prevention measures for falls, nutrition management) were not investigated in the enrichment design studies included. In addition, further triggers of adverse events, such as overdiagnosis or false-negative screening results, could not be evaluated with this design.

There was no restriction regarding study duration.

To identify relevant primary studies a 2-step approach was performed: In a first step, comprehensive, high-quality and up-to-date systematic reviews (SRs) / health technology assessments (HTAs) were searched for in a focused search covering the period from 2013 onwards in MEDLINE, the Cochrane Database of Systematic Reviews, and the Health Technology Database. The websites of HTA agencies were also searched (National Institute for Health and Care Excellence [NICE]), Agency for Healthcare Research and Quality (AHRQ). The AHRQ report on screening for osteoporosis fulfilled the eligibility criteria and was assessed as comprehensive; it was therefore included for the purpose of identifying primary studies [14]. In a second step, an update search for primary studies was conducted in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for the period not covered by the AHRQ report.

In addition, study registries were searched and enquiries were sent to authors of study publications.

The last search was performed on 13/05/2019.

The selection of relevant studies was carried out by 2 reviewers (1 from the authoring and 1 from the co-authoring team) independently of each other. Discrepancies were resolved by discussion between the 2 reviewers. Data were extracted into standardised tables.

The risk of bias was evaluated on the study and outcome level and classified as low, moderate, or high. The Cochrane risk-of-bias tool [15] was used according to the EUnetHTA Guideline on Internal Validity. After combining all data for a given outcome, a conclusion was drawn on the quality of the evidence with regard to the certainty of the observed effects (the quality was rated as either high, moderate, low or very low). Following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, different additional criteria for up- and downgrading the quality of evidence were applied.

Given that the studies were comparable with regard to the research question and relevant characteristics and no significant heterogeneity was observed, the individual study results were summarised quantitatively by means of meta-analyses.

Results

Results of the comprehensive information retrieval process

As part of the information retrieval process, 8 RCTs (3 RCTs with marker-based strategy design [16-18] and 5 RCTs with enrichment design [19-23]) were identified as relevant to the research question of the Rapid REA; 2 further studies were formally included [24,25], but not used for the assessment, because of a lack of extractable data. In addition, their sample size was small and their follow-up period short.

Furthermore, 1 ongoing study (SALT [26])[1], 1 study without reported results (POROS, [27]), and 1 small ongoing enrichment design study [28] were identified.

Available evidence

Characteristics of the studies included in the assessment

RCTs with marker-based strategy design

A total of 49,912 postmenopausal women between 65 and 85 years of age were examined in the strategy design RCTs and were randomly allocated to screening (n = 24,367) or no screening (n = 25,545). The 2 largest RCTs were the Danish ROSE trial [17] and the British SCOOP trial [16]. Both studies employed a similar 3-tiered screening approach consisting of a fracture risk assessment (FRAX score), BMD measurement (DXA) as well as anti-osteoporosis drug treatment according to local standards. In the ROSE trial, the participants (women between 70 and 85 years) were identified on the basis of a civil register and randomised before obtaining their consent to participate. In this way, the effectiveness of the introduction of a screening programme was investigated. In contrast, participants in the SCOOP trial (women between 65 and 80 years) were randomised only after their agreement to participate in the study, so that the effectiveness of the screening elements as such was investigated. The follow-up was 5 years in both trials. Different operationalisations of the outcome “fracture” were investigated in both trials. In addition, SCOOP reported results on mortality and HrQoL.

In the British COSHIBA trial [18] a different screening approach was chosen: 3,200 postmenopausal women between 65 and 80 years of age were allocated randomly to a screening and a control group after completing a questionnaire that collected baseline data. In the screening group, height

[1] The results of this study were published after our update search in May 2019 and could therefore not be included in this Rapid REA. Future assessments should take the results into account.

loss, history of previous non-vertebral fractures, the Margolis back pain score, and the rib-to-pelvis distance were assessed as risk factors. Women at a high risk of fracture were offered a lateral thoracolumbar spine radiograph. The type of treatment was left up to the attending general practitioner (GP). As a relevant outcome, self-reported fractures were assessed after a follow-up of 1 year.

RCTs with enrichment design

Five enrichment design RCTs were included as additional evidence. In 2 RCTs performed in the United States of America (USA) in the 1990s, postmenopausal women between 55 and 81 years of age were treated with either alendronate (n = 3,236) or placebo (n = 3,223). These 2 RCTs were the 2 sub-studies of the Fracture Intervention Trial (FIT): 1 sub-study (i.e. Clinical Fracture study [19]) included only women without pre-existing vertebral fractures but with a T-score of ≤ -2.5 standard deviations (SD), while the other sub-study (i.e. Vertebral Deformity study [20]) included only women with decreased BMD and with ≥ 1 pre-existing vertebral fracture(s). In the joint recruitment procedure, women from the general population were contacted by means of mass mailings and screened using DXA. Women were included in the study if the T-score was ≤ -1.6 SD. The 2 sub-studies provided data on fractures [19,20], back pain [20], utilisation of healthcare resources [20], mortality [19,20], and adverse events [19,20]. They are counted as 2 RCTs in this Rapid REA, as they were conducted and published separately after joint recruitment (for detailed information see Section 2.8).

In addition, an RCT from New Zealand (Reid 2018 [23]) was included. 2,000 postmenopausal women from the Auckland region were recruited using electoral registers. They were ≥ 65 years old and had a T-Score of -1.0 to -2.5 at either the total hip or the femoral neck on either side. They were randomly assigned to receive 4 infusions of either zoledronic acid at a dose of 5 mg or placebo at 18-month intervals. Follow-up was 6 years. The trial provided data on fractures, adverse events, and mortality.

In 2 further RCTs from China, postmenopausal women were randomly assigned to be either treated with once-yearly intravenous zoledronic acid or matching placebo after being recruited from the general population. In Liang 2017 [21], 285 women between 50 and 65 years were screened with DXA and a blood test prior to randomisation and were followed for 2 years. In Yang 2015 [22], only DXA testing was performed before randomisation of postmenopausal women (n = 100). Follow-up was 1 year. The trials provided evaluable data on adverse events [21], fractures [21,22], and mortality [22].

Overview of outcomes relevant for the assessment

Table 0-1 and Table 0-2 provide an overview of the available data on patient-relevant outcomes from the trials included.

In all but 2 studies included, a composite fracture-outcome was selected as a primary or secondary outcome.

The term "clinical fractures" covered the outcome combinations “any clinical fractures” (i.e. facial and skull fractures excluded as well as pathological fractures or fractures due to trauma sufficient to fracture a normal bone in most young adults), “any self-reported fractures”, and “symptomatic fractures” (symptomatic vertebral fractures and all non-vertebral fractures included, but pathological fractures excluded). The term “osteoporosis-related fractures” covered the outcome combinations “osteoporosis-related fractures” (i.e. all fractures excluding the hands, feet, nose, skull, or cervical vertebrae) and “all potential osteoporotic fractures” (i.e. all fractures excluding fractures of fingers, toes, skull, or face).

"Major osteoporotic fractures" covered fractures of the hip, spine, wrist, and humerus, while "other fractures" were defined as "other fractures than hip, forearm, and vertebral fractures". "Any non-vertebral fractures" included all fractures, excluding fractures of the spine. All patient-relevant fracture (sub-) outcomes are summarised under the umbrella term "symptomatic fractures".

Table 0-1: Matrix of patient-relevant outcomes in RCTs with marker-based strategy design

Study	Outcomes														
		Morbidity													
		Symptomatic fractures													
		Composite outcomes													
	Mortality	Any clinical fracture	Major osteoporotic fracture	Osteoporosis-related fracture	Clinical vertebral fracture	Other clinical fractures	Any non-vertebral fracture	Hip fracture	Wrist fracture	Back pain	HrQoL	Anxiety	Utilisation of healthcare resources	(Serious) adverse events	Overdiagnosis
RCTs with marker-based strategy design															
SCOOP [16]	■	■	-	■	-	-	-	■	-	-	■	□[a]	-	□[b]	-
ROSE [17]	-	-	■	■	-	-	-	■	-	-	-	-	-	-	-
COSHIBA [18]	-	■	-	-	■	■	-	■	■	-	-	-	-	-	-

■: data were reported and were evaluable
□: data were reported but were not evaluable
-: no data reported (no further data) / outcome not assessed
a: no data available for the entire intervention group
b: data were only assessed in the screening arm
Abbreviations: HrQoL: health-related quality of life

Table 0-2: Matrix of patient-relevant outcomes in RCTs with enrichment design

Study	Outcomes														
		Morbidity													
		Symptomatic fractures													
		Composite outcomes													
	Mortality	Any clinical fracture	Major osteoporotic fracture	Osteoporosis-related fracture	Clinical vertebral fracture	Other clinical fractures	Any non-vertebral fracture	Hip fracture	Wrist fracture	Back pain	HrQoL	Anxiety	Utilisation of healthcare resources	(Serious) adverse events	Overdiagnosis
RCTs enrichment design															
Vertebral Deformity study, FIT (Black 1996) [20]	■	■	-	-	■	■	□[a]	■	■	■	-	-	■	■	-
Clinical Fracture study, FIT (Cummings 1998) [19]	■	■	-	-	■	■	□[a]	■	■	-	-	-	-	■	-
Liang 2015 [21]	-	■	-	-	-	-	-	-	-	■	-	-	-	■	-
Reid 2018 [23]	■	■	-	-	■	-	□[a]	■	■	-	-	-	-	■	-
Yang 2015 [22]	■	■	-	-	-	-	-	-	-	-	-	-	-	□[c]	-

■: data were reported and were evaluable
□: data were reported but were not evaluable
a: no corresponding results on this outcome were reported in studies with marker-based strategy design
b: operationalised as non-vertebral fragility fracture, excluding fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible.
c: data were not reported separately for intervention and control group
-: no data reported (no further data) / outcome not assessed
Abbreviations: HrQoL: health-related quality of life

Clinical effectiveness

Mortality (D0001)

Results for mortality were available from the SCOOP trial [16]. There was no statistically significant difference between the 2 study arms with respect to this outcome.

Mortality was also reported in 4 enrichment design RCTs [19,20,22,23]. No statistically significant difference could be observed between the 2 study arms in either (sub-) study.

Conclusion on benefit regarding mortality

Screening for osteoporosis results in little or no difference in mortality compared with no screening. This conclusion is based on high quality evidence.

Symptomatic fractures (D0005**)**

This operationalisation includes all fracture (sub-) outcomes assessed.

The evidence on this outcome is based on data from all 3 strategy design RCTs included (SCOOP [16], ROSE [17], and COSHIBA [18]). For all fracture (sub-) outcomes investigated, no advantage could be derived in favour of the intervention. Regarding hip fractures, the evidence was inconclusive.

Additional evidence primarily came from the 2 sub-studies of the FIT trial (Clinical Fracture study, Cummings 1998 [19], Vertebral Deformity study, Black 1996 [20]) and from Reid 2018 [23]. However, the evidence was too weak to influence the findings of the strategy design studies.

Subgroup analyses

According to the specifications given in the Project Plan, the factors age, sex, BMI, and ethnicity were examined for possible effect modification. In addition, it was checked whether it was possible to examine other factors, such as history of post-menopausal fractures and influence of the calculated fracture risk (using a risk assessment tool with or without additional BMD).

Subgroup analyses from strategy design studies were not available. However, in a secondary analysis by Reid 2018 [29] the anti-fracture effect of zoledronic acid was investigated in subgroups. The analysis showed that the positive influence of zoledronic acid on the reduction in fractures was largely consistent across the cohort investigated. None of the potential effect modifiers showed statistically significant interactions.

Conclusion on benefit regarding symptomatic fractures

Screening for osteoporosis probably results in little or no difference in the incidence of symptomatic fractures compared with no screening. This conclusion is based on moderate-quality evidence.

The baseline variables investigated (age, anthropometry, BMI, dietary calcium intake, baseline fracture status, recent falls history, BMD, and calculated fracture risk) may have little or no influence on the effectiveness of screening. This conclusion is based on low-quality evidence.

Back pain (D0011**,** D0016**)**

No data from studies with marker-based strategy design were available.

In the Vertebral Deformity study of the FIT trial (women with pre-existing vertebral fractures [20]), the outcome was assessed using several different operationalisations. Both the reduction in the number of bed-rest days due to back pain and the reduction in the number of limited activity days due to back pain were statistically significant in favour of the intervention group. However, no statistically significant effects were shown for other operationalisations.

Conclusion on benefit regarding back pain

It is uncertain whether screening for osteoporosis improves back pain. This conclusion is based on evidence of very low quality.

Health-related quality of life (D0012**)**

Data on HrQoL were available from the SCOOP trial [16].

The HrQoL was measured by means of the EQ-5D and SF-12 for mental health as well as the SF-12 for physical health after 60 months of follow-up. For all 3 HrQoL instruments, no statistically significant difference between the 2 study arms was found.

Conclusion on benefit regarding health-related quality of life

Screening for osteoporosis probably results in little or no difference in HrQoL compared with no screening. This conclusion is based on moderate-quality evidence.

Utilisation of healthcare resources

No data from studies with marker-based strategy design were available for the outcome "utilisation of health care resources". Data from enrichment design studies were additionally consulted. In the Vertebral Deformity study of the FIT trial (women with pre-existing vertebral fractures [20]), the outcome was assessed using different operationalisations. A limitation of these operationalisations was that only fracture-related utilisation of healthcare resources was reported. While there was no statistically significant difference for overall hospital stays or stays in nursing homes / rehab, the authors found a statistically significant reduction in favour of the intervention group in the fracture-related use of all resources and in the number of emergency room visits.

Conclusion on benefit regarding utilisation of healthcare resources

It is uncertain whether screening for osteoporosis lowers fracture-related utilisation of healthcare resources. This conclusion is based on evidence of very low quality.

Safety

(Serious) adverse events (C0008**)**

Data on (serious) adverse events were not reported adequately in the strategy-design RCTs. While this outcome was not reported at all in ROSE and COSHIBA, in SCOOP “GPs were [only] asked to record any adverse events related to the screening process” [16]. Therefore, it was only possible to extract (serious) adverse events from studies with enrichment design. Both the 2 sub-studies of the FIT trial [19,20] (Vertebral Deformity study [20], Clinical Fracture study [19]), as well as Reid 2018 [23] and Liang 2015 [21], reported (serious) adverse events. However, 2 different drugs were examined in different dosage forms and with different durations of use. In addition, the quality of the evidence differed in these studies. Therefore, the studies were considered separately, where deemed necessary.

Alendronate

Adverse events resulting in hospital admission were assessed in both sub-studies of the FIT trial. While no statistically significant difference was observed in the Clinical Fracture study [19], adverse events resulting in hospital admission were significantly more common in the placebo than the alendronate group in the Vertebral Deformity study [20]. Similar proportions of women in the intervention and control arms of the 2 sub-populations of the FIT trials permanently discontinued study medication because of adverse events related to upper gastrointestinal tract symptoms. Similar rates between the intervention and control arms were reported in the 2 FIT sub-trials for upper gastrointestinal tract symptoms or events, as well as for gastric or duodenal perforations, ulcers and bleeding,

and oesophageal and serious oesophageal events. The same applied to the rates for atrial fibrillation and severe atrial fibrillation.

Zoledronic acid

In Reid 2018 [23], zoledronic acid was administered at 18-month intervals and follow-up was 6 years. The overall rate of serious adverse events showed an advantage for the intervention group, which was marginally not statistically significant but included fractures that resulted in hospitalisation. An overall rate for adverse events was not reported. No statistically significant differences in other serious adverse events were observed. Common adverse effects that may occur shortly after administration of intravenous zoledronic acid, such as flu-like symptoms, headache or gastrointestinal symptoms, were not among the pre-specified adverse effects and were not reported.

No serious adverse events occurred in Liang 2017 [21] within the follow-up of 2 years. Adverse events were only reported if they occurred within 3 days after drug administration and in more than 5 % of patients. The quality of information was therefore limited. An overall rate of adverse events was not reported. The effect on unspecific adverse events, such as influenza-like illness, pyrexia, and myalgia, was large and occurred significantly more often in the intervention group than in the control group. It was stated that “the most common post-dose symptom adverse events were generally mild to moderate in intensity and were of short duration (the majority lasting 3 days or less)”.

Conclusion on harm regarding (serious) adverse events

As only data from enrichment design studies could be used to assess (serious) adverse events due to screening for osteoporosis, the quality of the evidence was downgraded by 2 levels due to indirectness. Since in addition, the risk of bias was high in the study pool investigating alendronate, the quality of the evidence was consequently rated as “very low” for this outcome if alendronate formed part of the screening-treatment approach. It is uncertain to what extent adverse effects occur if alendronate is administered.

Data from Reid 2018 indicate that screening for osteoporosis in postmenopausal women may result in little or no difference in the rate of serious adverse events if zoledronic acid (administered intravenously in 18-month intervals) forms part of the screening-treatment strategy within the follow-up of 6 years. This conclusion is based on low-quality evidence. Data on short-term adverse events were reported by Liang 2017. However, these were only assessed within a timeframe of 3 days after drug administration and only if they occurred in more than 5 % of the participants. Although the observed effects were very large, the risk of bias was high and the ITT principle was not adequately implemented, which is why the extent of short-term adverse events is uncertain if zoledronic acid forms part of the screening-treatment strategy. This conclusion is based on evidence of very low quality.

Overdiagnosis

An estimation of the frequency or proportion of overdiagnoses caused by osteoporosis screening was not possible, as no data on this outcome were identified.

Upcoming evidence and studies without reported results

A total of 2 strategy design RCTs without reported results were identified: POROS and SALT.

The **POROS study** [27] was conducted in the western United States and probably completed in 2012. 1,836 women between 50 and 65 years of age were stratified into 2 groups after filling in a self-administered questionnaire on baseline characteristics and fracture risk factors. While the women without risk factors were assigned to "usual care", the women with ≥ 1 risk factor were allocated randomly in a 4:1 ratio to the intervention or control arm. The control group (n = 372)

received usual care, while the women in the intervention group (n = 1,464) underwent a 2-step screening consisting of a urine test and, if necessary (i.e. if a certain threshold value was exceeded in the urine test), subsequent DXA. Afterwards they received usual care from their family doctor. Incident patient-reported fractures were to be collected after 24 months of follow-up. In addition, the association between incidence of fractures and number and type of fracture risk factors was to be investigated. No study registry entry was identified for this trial. An enquiry to the authors regarding the unclear status of the study was not answered. This situation is concerning because of possible publication bias.

The **SALT study** [26][2], which started in the Netherlands in 2010, aimed to randomly allocate about 1,700 women aged 65 to 90 years from participating GPs into intervention and control arms. According to the original registry entry, the study should have been completed in 2016 but the publication of the protocol (from 2017) reported delays in recruitment. According to the revised registry entry in 2017 [30], recruitment was incomplete. At the start of the study, the women answer a self-administered questionnaire. If they have ≥ 1 clinical risk factor for fractures (the screening programme includes an adapted FRAX tool), they are allocated randomly to either the screening arm or the control arm. The women in the screening arm receive a BMD (DXA and instant vertebral assessment [IVA]), a risk assessment for falls, and chemistry screening, while women in the control arm receive usual care. According to predefined treatment thresholds, treatment instructions are given to the GP. The primary outcome is the time to new fracture and the number of fractures in high risk-individuals after 36 months of follow-up. Secondary outcomes are time to new fracture after the end of follow-up (54 months), the number of fractures after 36 months, deaths, and falls. Since this author enquiry was also not answered, it could not be clarified whether and when results of this study can be expected.

In the course of the search in study registries, the registry entry of a small ongoing enrichment design study from Sri Lanka was identified (**SLCTR/2018/038** [28]). This study investigates the effect of alendronate (70 mg / week) and vitamin D3 (800 IU / day) on selected bone turnover markers in women with postmenopausal osteoporosis and a high fracture risk (assessed with FRAX and BMD values). The study aims to recruit a total of 60 newly diagnosed women using electoral registers. Follow-up is 24 weeks. The patient-relevant outcome is adverse events. The anticipated end date is November 2019. Since the sample size is very small, the influence of the study results on the results of the present Rapid REA appears to be negligible.

***Reimbursement** [B0003]*

Screening for osteoporosis is generally not reimbursed in Europe. In some EU countries, opportunistic screening is offered to identify people at a high risk of fractures. However, Poland is currently planning a national screening programme for osteoporosis, which is due to be launched in 2023.

[2] The results of this study were published after our update search in May 2019 and could therefore not be included in this Rapid REA. Future assessments should take the results into account.

Table 0-3: Summary of findings table of screening for osteoporosis in postmenopausal women

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
Symptomatic fractures Data from **3 MB-SD RCTs** presented	Clinical fractures in 5 years 151 per 1000 [139; 165]	Clinical fractures in 5 years 160 per 1000[a]	Clinical fractures HR: 0.94, [0.86; 1.03] [16] OR: 0.6, [0.35; 1.03] [18]	15,683 (2, MB-SD)	High ++++	Screening for osteoporosis has probably little or no effect on the incidence of symptomatic fractures. This conclusion is based on overall moderate-quality evidence. 3 strategy design RCTs reported fractures. Results were reported for various types of fractures and the broadest and most commonly used operationalisations are being reported here. However, due to either heterogeneity or content issues, it was not always possible to pool these data. The corresponding evidence from enrichment design studies was too weak to influence the observed effects of strategy design studies (data not shown).
	Osteoporosis-related fractures in 5 years 131 per 1000[b] [125; 137]	Osteoporosis-related fractures in 5 years 132 per 1000[b]	Osteoporosis-related fractures HR: 0.99, [0.94; 1.04][c] [16,17]	46,712 (2, MB-SD)	High ++++	
	Hip fractures in 5 years 25 per 1000[d] [21; 31] 31 per 1000[e] [28; 35]	Hip fractures in 5 years 35 per 1000[f] 31 per 1000[g]	Hip fractures HR: 0.72, [0.59; 0.89] [16] SHR: 1.01, [0.89; 1.14] [17] OR: 1.01, [0.25; 4.71][h] [18]	49,912 (3, MB-SD)	Moderate +++O (downgraded due to inconsistency[i])	

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
Back pain Data from **1 ED RCT** presented	Not estimable	Not estimable	≥ 7 bed rest day(s) due to back pain RR: 0.44, [0.30; 0.64][j] [31] New or worsened disability due to back pain RR: 0.85, [0.63; 1.15][j] [31] Data on changes compared to start of study on several operationalisations of number of days with back pain: not available	2,027 (1, ED)	Very low +OOO (downgraded due to a high risk of bias and indirectness[i])	It is uncertain whether screening for osteoporosis improves back pain. In total, results on different operationalisations from 2 different enrichment design studies were available for this outcome. Only the weakest and strongest effects are shown here.
Utilisation of healthcare resources Data from **1 ED RCT** presented	Not estimable	Not estimable	Utilisation of healthcare resource OR: 0.73, [0.54; 0.98][j] [32] Utilisation of emergency room OR: 0.70, [0.52; 0.96][j] [32] Utilisation of hospital OR: 0.73, [0.47; 1.13][j] [32] Utilisation of nursing home / rehab OR: 0.65, [0.33; 1.29][j] [32]	2,027 (1, ED)	Very low +OOO (downgraded due to a high risk of bias and in-directness[k])	It is uncertain whether screening for osteoporosis lowers the fracture-related utilisation of healthcare resources. In total, results on different operationalisations from 1 enrichment design study were available for this outcome.

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
(Serious) adverse events Data from **4 ED RCTs** presented	Not estimable	Not estimable	Any gastric or duodenal perforations, ulcers, and bleeding RR: 0.86, [0.59; 1.24][l] [33] Discontinuation of study medication due to upper GI tract symptoms RR: 1.15, [0.87; 1.54][l] [33] Serious atrial fibrillation RR: 1.51, [0.97; 2.40][l] [34]	6,459 (2, ED, assessing alendronate)	Very low +OOO (downgraded due to high risk of bias and indirectness)	Alendronate It is uncertain to what extent side effects occur if alendronate forms part of the screening-treatment strategy. 2 enrichment design studies (FIT trials, [19,20]) reported no difference in (serious) adverse events. As no overall rate of (serious) adverse events was reported, only those adverse events that were deemed most relevant are shown here.
			Serious adverse events[m] OR: 0.84, [0.70;1.00] [23] Composite of vascular events[n] OR: 0.76, [0.52;1.09] [23] Atrial fibrillation OR: 0.98, [0.67; 1.44] [23] Myocardial infarction OR: 0.61, [0.36; 1.02] [23]	2,000 (1, ED, assessing zoledronic acid)	Low ++OO (downgraded due to indirectness)	Zoledronic acid Screening for osteoporosis in postmenopausal women may result in little or no difference in the rate of serious adverse events if zoledronic acid (administered intravenously in 18-month intervals) forms part of the screening-treatment strategy. The 4 most common serious adverse events are presented here.

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
			Headache (influenza-like illness) OR: 0.729, [1.67; 31.38] [21] Pyrexia OR: 11.77, [3.45; 39.19] [21] Myalgia OR: 6.39, [2.19; 18.66] [21] Arthralgia OR: 1.79, [0.85; 3.74] [21]	250 (1, ED, assessing zoledronic acid)	Very low +OOO (downgraded due to high risk of bias and in-directness)	Zoledronic acid The extent of short-term adverse events is uncertain if zoledronic acid forms part of the screening-treatment strategy. 1 enrichment design study stated that no serious adverse events occurred, but reported a difference in 3 days post-dose mild side effects to the detriment of the intervention that occurred in more than 5 % of participants [21].
			No studies were found that looked at screening strategies using other drugs than alendronate or zoledronic acid.			
Mortality Data from **1 MB-SD RCT** presented	Mortality in 5 years: 88 per 1000[o] [78; 99]	Mortality in 5 years: 84 per 1000[p]	HR: 1.05, [0.93; 1.19] [16]	12,483 (1, MB-SD)	High ++++	Screening for osteoporosis results in little or no difference in mortality. Effect from 1 strategy design RCT Evidence from enrichment design studies was too weak to support the effects of strategy design studies (data not being shown here)

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
Health-related quality of life Data from **1 MB-SD RCT** presented	Not estimable	Not estimable	EQ-5D Mean Score I-Group: 0.63 (0.33[q]) Mean Score C-Group: 0.63 (0.32[q]) Difference: p = 0.154 [16] SF-12 (physical health) Mean Score I-Group:38.3 (16.7[q]) Mean Score C-Group: 38.3 (16.6[q]) Difference: p = 0.237 [16] SF-12 (mental health) Mean Score I-Group:46.0 (18.3[q]) Mean Score C-Group: 46.3 (18.2[q]) Difference: p = 0.554 [16]	12,483 (1, MB-SD)	Moderate +++O (downgraded by 1 levels for high risk of bias)	Screening for osteoporosis probably results in little or no difference in HrQoL. 1 strategy design study reported no statistically significant difference in HrQoL (assessed with EQ-5D, SF-12 [mental health] and SF-12 [physical health]).

Outcome Number and design of the studies whose results are presented	**Anticipated absolute effects [95% CI]**		**Relative effect [95% CI]**	**Number of postmeno-pausal women (studies, design)**	**Quality**	**Comments**
	Risk with screening	**Risk without screening**				
a: assumption of baseline risk for clinical fractures after 5 years taken from SCOOP: 0.16 b: absolute risks for major osteoporotic fractures after 5 years obtained by naïve pooling of results from SCOOP and ROSE c: relative effect from meta-analysis (Rapid REA authors` own calculation) d: assumption of baseline risk for hip fractures after 5 years is calculated via HR e: assumption of baseline risk for hip fractures after 5 years is calculated via SHR f: assumption of baseline risk for hip fractures after 5 years taken from SCOOP: 3.5 % g: assumption of baseline risk for hip fractures after 5 years taken from ROSE: 3.1 % h: absolute risks were only estimated for the 2 largest screening RCTs ROSE and SCOOP i: the quality of evidence is downgraded by 1 level for inconsistency (I^2 = 87.0 %, differences in study design) j: data refer to population of the Vertebral Deformity study [20] k: the quality of evidence is downgraded due to a high risk of bias and indirectness (enrichment design) l: data refer to entire FIT population (Vertebral Deformity study [20] and Clinical Fracture study [19]) m: included hospitalisation due to fractures n: sudden death, myocardial infarction, coronary artery revascularisation, or stroke o: assumption of baseline risk for mortality after 5 years taken from SCOOP: 8.8 % (I-group) p: assumption of baseline risk for mortality after 5 years taken from SCOOP: 8.4 % (C-group) q: SD **Abbreviations:** C-Group: control group; CI: confidence interval; ED: enrichment design; GI: gastro-intestinal; HR: hazard ratio; I-Group: intervention group; MB-SD: marker-based strategy design; no.: number; OR: odds ratio; REA: relative effectiveness assessment; RR: relative risk, SD: standard deviation; SHR: sub-hazard ratio						

Discussion

The main finding of this Rapid REA is that screening for osteoporosis in postmenopausal women offers no (or only a small) advantage with regard to symptomatic fractures. The operationalisation “symptomatic fractures” covered all clinical fractures that presumably were experienced as symptomatic by the patient. This result mainly came from 3 "conventional" screening studies, i.e. strategy design studies. In addition, 5 enrichment design studies had been included that investigated a narrower research question, namely whether it is beneficial to treat patients (recruited from the general population) who were tested positive by screening. These studies were primarily consulted to assess possible adverse effects of screening, which were expected to be inadequately investigated by strategy design studies. However, the evidence from these studies was considered to be weak, mainly due to their indirectness. Nevertheless, data from 1 enrichment design study indicate that a screening-treatment strategy for osteoporosis including zoledronic acid may result in little or no difference in the rate of serious adverse events compared with no screening. The effect on short-term adverse events is uncertain. The same applies to a screening-treatment strategy including alendronate regarding adverse and serious adverse events. No conclusion can be drawn for (serious) adverse events of non-drug anti-osteoporosis treatment. Moreover, due to a lack of data, it is not possible to assess whether there is a link between potential harm and a certain screening interval or a certain setting. The studies included failed to describe whether specific subgroups of postmenopausal women had a higher risk of (serious) adverse events. In addition, no data were available to assess generic disease-specific quality of life.

In all studies included, the participants were postmenopausal women (in the 2 largest screening RCTs, women were aged between 70 and 85 [16] and 65 and 80 years [17]). While this is understandable and meaningful, as the prevalence of osteoporosis is highest in this population, this means that no evidence is available on screening of men or younger women. Due to these differences in prevalence and due to a lack of available data, no conclusion can be drawn for other populations.

The 2 most important and largest conventional screening studies included investigated FRAX and subsequent DXA as a screening approach. FRAX is a computer-based algorithm to assess the risk of fractures. However, since among other things the underlying algorithms of FRAX vary from country to country (but are not publicly accessible) and different treatment thresholds are used in different countries, it is unclear whether FRAX always identifies sufficiently similar patients. In the ROSE study, the majority of the prescribed anti-osteoporosis drugs were bisphosphonates [35]. Whether and to what extent further anti-osteoporosis measures were recommended and implemented remained unclear for both the ROSE and SCOOP studies. The treatment decision was up to the GP. Nevertheless, the findings of this Rapid REA are in principle considered to be applicable to the European context, but presumably not to alternative screening strategies.

Conclusion

Since the available studies of moderate quality show no effect of screening on the incidence of symptomatic fractures, screening for osteoporosis in postmenopausal women probably has little or no benefit. These findings are mainly based on studies investigating a screening strategy using FRAX for risk assessment and DXA for BMD measurement. The studies included did not allow the evaluation of screening strategies based on other screening tools. As in any screening intervention, benefits and harms are affected by multiple factors such as the type and uptake of screening and treatment. No studies were found on osteoporosis screening in men or younger women.

1 SCOPE

Description	Project Scope	
	Marker-based strategy design "Conventional screening study" Rationale for inclusion: answer the research question of the Rapid REA: Does screening for osteoporosis in the general population offer an advantage over no screening with regard to patient-relevant outcomes?	Enrichment design (additional evidence; limited to RCTs comparing anti-osteoporosis drug treatment with no drug treatment or placebo) Rationale for inclusion: enrichment design RCTs are mainly included because it is assumed that conventional screening studies do not report relevant outcomes such as adverse events.
Population	Target population[a]: general population	Patients who were i) selected from the target population[a] ii) newly diagnosed with osteoporosis using a clinical risk assessment tool and / or BMD measurement (DXA, qUS, qCT)
Intervention	Screening for osteoporosis using • clinical risk assessment tools (e.g. FRAX) and/or • BMD measurement (DXA, qUS or qCT) followed by drug treatment (as described in the section "*Anti-osteoporosis drug treatment*", Table 2-5) and / or non-drug measures to prevent osteoporotic fractures.	Anti-osteoporosis drug treatment (as described in the section "*Anti-osteoporosis drug treatment*", Table 2-5)
Comparison	No screening	No treatment, placebo

Description	Project Scope
Outcomes	Effectiveness- and safety-related: Critical outcome[b]: • symptomatic fractures Important outcomes[b]: • mortality (overall and fracture-related) • HrQoL • pain • body function and activities of daily living • use of resources (visits to doctors and hospitals, admission to nursing homes) • adverse events • As screening is prone to overdiagnosis and consequently to overtreatment, the project also aims to quantify the proportion of overtreatment among those who receive treatment
Study design	RCTs: marker-based strategy designs, enrichment designs (limited to RCTs comparing anti-osteoporosis drug treatment with no drug treatment or placebo); no marker-by-treatment interaction designs For illustration, please see Figure 8, Figure 9 and Figure 10 in Appendix 1.
a: Target population: general population (women and / or men, different age groups, countries, etc.). Selected patient groups at increased risk of osteoporosis (e.g. patients with a [previous] osteoporotic fracture, organ transplant receivers, patients with cystic fibrosis, inflammatory bowel disease, etc.) are excluded. b: Description of the importance of the outcomes according to GRADE [36] **Abbreviations:** BMD: bone mineral density measurement; DXA: dual-energy x-ray absorptiometry; FRAX: Fracture Risk Assessment Tool; HrQoL: health-related quality of life; RCT: randomised controlled trial; qCT: quantitative computed tomography; qUS: quantitative ultrasound	

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The scope of this Rapid REA is to investigate whether screening in the general population offers an advantage over no screening with regard to patient-relevant outcomes.

The scope stipulates that in addition to studies with marker-based strategy design, studies with enrichment design should also be included. The rationale for including them was mainly due to the assumption that adverse events resulting from anti-osteoporosis treatment is not reported adequately in conventional screening studies. For pragmatic reasons, only enrichment design studies limited to drug treatment were included in this report. Further treatment options (e.g. preventive measures for falls, nutrition management) as well as further triggers for adverse events such as overdiagnosis or a false-negative screening result are not investigated in the included studies of this design and research question.

The respective comparators (“no screening” and “no treatment / placebo”) were chosen because there is currently no universally accepted policy for population-based screening in Europe. No treatment / placebo reflects the current situation in European countries, as people with asymptomatic and undiagnosed osteoporosis do not receive any anti-osteoporosis medication.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

Description of the distribution of responsibilities and the workload between authors and co-authors:

IQWiG (author)

- Develop the first draft of the EUnetHTA Project Plan; amend and supplement the Project Plan according to the review by co-authors and dedicated reviewers as well as comments of external experts.
- Perform the information retrieval (including study selection), data extraction and risk of bias assessment of the references selected, perform the assessment of the quality of the body of evidence, discuss potential discrepancies with the co-author and reach a consensus.
- Fill in the checklist regarding potential ethical (ETH), organisational (ORG), social (SOC) and legal (LEG) aspects of the HTA Core Model® for Rapid REA
- Prepare the author`s reply of the comments on the first and second draft Project Plan and the first and second draft REA provided by dedicated reviewers and external experts.
- Review answers of assessment elements on the TEC and CUR domains, discuss potential discrepancies with the co-author and reach a consensus
- Send draft versions to reviewers, compile feedback from reviewers and make plausible changes according to reviewers' comments
- Prepare the final assessment and write the executive summary of the assessment

SNHTA (co-author)

- Review and comment on the first draft Project Plan.
- Check and approve all steps (e.g. data extraction, risk of bias assessment, quality of the body of evidence assessment).
- Perform study selection as the second screener.
- Answer the questions of the assessment elements of the TEC and CUR domains within the framework of the first draft REA
- Collaborate in the writing of the discussion and conclusions and approve these sections.
- Review and comment on the draft assessment, propose amendments where necessary (conduct an additional manual search of the literature if needed) and provide written feedback.
- Prepare the co-author`s reply of the comments of the first and second draft REA provided by dedicated reviewers and external experts on issues related to the TEC and CUR domains.

2.2 Source of assessment elements

The selection of assessment elements was based on the EUnetHTA Core Model for Rapid Relative Effectiveness Assessments (REA, Version 4.2) [37]. The selected assessment elements with generic questions were translated into research questions (answerable questions, see the summary and Sections 4, 5, 6). The checklist for potential ethical, organisational, patient and social, and legal aspects of the HTA Core Model for Rapid REA was also filled in (see Appendix 3).

2.3 Search

TEC and CUR domains

The information retrieved for the TEC and CUR domains was based on:

- current clinical guidelines and systematic or narrative reviews, which were identified on the basis of an exploratory search,
- input from clinical experts, particularly related to the description of disease, current treatment, current use of screening elements and drug and non-drug treatment, and the best available epidemiological data. The clinical experts were asked to verify the relevance and accuracy of the information and citations,
- input from other HTA agencies on the current use of the technology via a survey.

The evaluation and comparison of the effectiveness of the large number of devices (in particular DXA) and drugs available for diagnosing and treating low BMD, which may be part of the subsequent management after the initial risk assessment, is not the primary objective of this Rapid REA. Even though the subsequent management of low BMD will affect the effectiveness of any screening, the decision was made that a comprehensive review of the CE status and marketing authorisation of all of the drugs and devices currently available for the diagnosis and treatment of patients with osteoporosis would be very time consuming and of very limited practical use. Such a review was therefore not undertaken.

EFF and SAF domains

A 2-step approach was performed with the aim of producing results efficiently and using the available scientific evidence of the highest level.

Step 1) In a first step SRs / HTAs were searched for in a focused search covering the period from 2013 onwards.

The aim of the focused search was to achieve a balanced relationship between sensitivity (i.e. completeness) and precision (i.e. accuracy), with a sensitivity of more than 80 %.

The procedure with regard to the development of the search strategy, quality assurance, conduct of the search, study selection and documentation is comparable to the search in bibliographic databases (see Step 2). However, restrictions or adjustments were made in the areas of database selection, selection of study filters, restriction of search period (2013 to 2018) and study selection (performed by 1 reviewer and quality assured by a second reviewer).

When searching for SRs, it was considered sufficient to identify a large part of the high-quality and up-to-date SRs on the research question. If SRs / HTAs fulfilled the inclusion criteria of the Rapid REA, the quality of information retrieval (including methods used for study selection) was checked in these documents. This means that the SRs / HTAs met the requirements of Item 3 of the AMSTAR checklist [38].

If SRs / HTAs fulfilled the inclusion criteria of the Rapid REA, the quality of information retrieval (including methods used for study selection) was checked in these documents. The aim was to find comprehensive, high-quality and up-to-date SRs / HTAs from which primary studies were identified. In this procedure, the primary studies identified in SRs / HTAs were used for data extraction and assessment.

Step 2) In a second step, an update search was conducted for primary studies for the period not covered by the SRs / HTAs. Information sources listed in the Project Plan, but not considered in the

SRs / HTAs (e.g. study registries), were searched within the framework of the information retrieval for the Rapid REA.

Sources of information retrieval for SRs / HTAs (focused, Step 1)

Bibliographic databases

- MEDLINE
- Cochrane Database of Systematic Reviews
- Health Technology Assessment Database

Of the 209 SRs / HTAs identified, 202 were excluded as irrelevant in the title and abstract screening. 7 SRs / HTAs were deemed potentially relevant and obtained in full text. The Agency for Healthcare Research and Quality (AHRQ) report [14] met all inclusion criteria and was therefore evaluated with regard to its quality of information retrieval (see Table A-1). The SR´s information retrieval was assessed as comprehensive and therefore included for the purpose of identifying primary studies.

55 primary studies could be extracted from the AHRQ report, which were then examined to what extent they fulfilled the inclusion criteria of this Rapid REA (see section “Study selection”).

The search strategies for SRs / HTAs in bibliographic databases are displayed in Appendix 1. The search was performed on 12 July 2018.

Websites of HTA agencies

In addition, the websites of HTA agencies (NICE, AHRQ) were searched for SRs. No further relevant SRs / HTAs were identified that could not be found by searching bibliographic databases.

Sources of information retrieval for primary studies (comprehensive, Step 2)

Bibliographic databases (update search)

- MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials

The search strategies for bibliographic databases are displayed in Appendix 1. The last search was performed on 13 May 2019.

The PRESS (Peer Review of Electronic Search Strategies) checklist was used for the quality check of the search strategies [39].

Study registries

- U.S. National Institutes of Health. Clinical Trials.gov
- World Health Organisation. International Clinical Trials Registry Platform Search Portal
- European Medicines Agency. EU Clinical Trials Register

The search strategies for study registries are displayed in Appendix 1. The last search was performed on 13 May 2019.

Further sources of information and search techniques

Relevant studies or documents identified via further information sources and search techniques are only presented below if not already identified in primary information sources.

- Queries to authors

In order to clarify essential issues for missing data, authors of publications of potentially relevant studies were contacted by the main author of the Rapid REA (via e-mail, if the e-mail address is available in the publication). Queries were only sent out if the questions were likely to have a direct impact on the assessment's conclusion. The contents of the requests can be found in Appendix 4. No answers were received.

- Exploratory searches

Initially, only 1 sub-study of the FIT trial was identified (Vertebral Deformity study [20]). Therefore, an exploratory search was conducted and further publications on the FIT trial were identified [19,20,31-34,40-81].

Publications on the COSHIBA trial [18,82], Yuksel 2009 [24,83] and the design publications of ROSE [84], SCOOP [85], and Yuksel 2009 [86] were also identified.

In addition, the publication of the protocol of the unpublished POROS study [27] was identified by checking the reference list of a study included. The study publication of Reid 2018 [23] was identified by checking the respective registry entry.

Inclusion criteria

The following tables list the criteria that studies must meet in order to be included in the Rapid REA.

Table 2-1: Inclusion criteria for marker-based strategy design RCTs

Inclusion criteria for marker-based strategy design RCTs	
I 1	Population: General population (any age or sex)
I 2	Intervention: Screening for osteoporosis using a clinical risk assessment tool and/or BMD measurement (DXA, qUS, qCT) followed by drug (see section "*Anti-osteoporosis drug treatment*") and/or non-drug treatment
I 3	Comparison: no screening
I 4	Patient-relevant outcomes as defined in Table 2-6
I 5	RCT (marker-based strategy design)
I 6	Full publication available[a]
a: In this context, both a full clinical study report, as well as a report on a study that meets the criteria of CONSORT [87] and allows evaluation of the study, are considered to be full publications, insofar as the information provided on the study methods and results is not confidential. **Abbreviations:** BMD: bone mineral density; CONSORT: Consolidated Standards of Reporting Trials; RCT: randomised controlled trial; qUS: quantitative ultrasound, qCT: quantitative computed tomography	

Table 2-2: Inclusion criteria for enrichment design RCTs (additional evidence)

Inclusion criteria for enrichment design RCTs	
I 1	Population: patients who i) were selected from the general population and ii) were newly diagnosed with osteoporosis using a clinical risk assessment tool and/or bone density measurement (DXA, qUS, qCT)
I 2	Intervention: anti-osteoporosis drug treatment (as described in the section "*Anti-osteoporosis drug treatment"* below)
I 3	Comparison: placebo, no treatment
I 4	Patient-relevant outcomes as defined in Table 2-6
I 5	RCT (enrichment design)
I 6	Full publication available[a]
a: In this context, both a full clinical study report, as well as a report on a study that meets the criteria of CONSORT [87] and allows evaluation of the study, are considered to be full publications, insofar as the information provided on the study methods and results is not confidential. **Abbreviations:** CONSORT: Consolidated Standards of Reporting Trials; RCT: randomised controlled trial; qUS: quantitative ultrasound, qCT: quantitative computed tomography	

Anti-osteoporosis drug treatment

According to the current European guidance [1], the following active substances are considered to be major drug interventions:

1.) selective oestrogen-modulators (SERMs)
   a. raloxifene
   b. bazedoxifene
2.) bisphosphonates
   a. alendronate
   b. risedronate
   c. ibandronate
   d. zoledronic acid
3.) peptides of the parathyroid hormone family
   a. parathyroid hormone (PTH)
   b. teriparatide
4.) denosumab

Procedures in the event of a change in approval status during the assessment phase

If changes in the approval status of the interventions to be assessed occur during the course of the project, the criteria for the study inclusion may be adapted to the new conditions of approval. The changes made will be explicitly noted in the Rapid REA.

Inclusion of studies that do not fulfil the aforementioned criteria

For the inclusion criteria I1 (population), I2 (test intervention, in relation to the intervention group of the study), and I3 (control intervention, in relation to the control group of the study), it is sufficient if at least 80 % of the patients included meet these criteria. If appropriate subgroup analyses are available for such studies, these analyses are used. Studies in which the inclusion criteria I1, I2 and I3 are met in less than 80 % of the patients included will only be considered if subgroup analyses are available for patients who meet the inclusion criteria [88].

2.4 Study selection

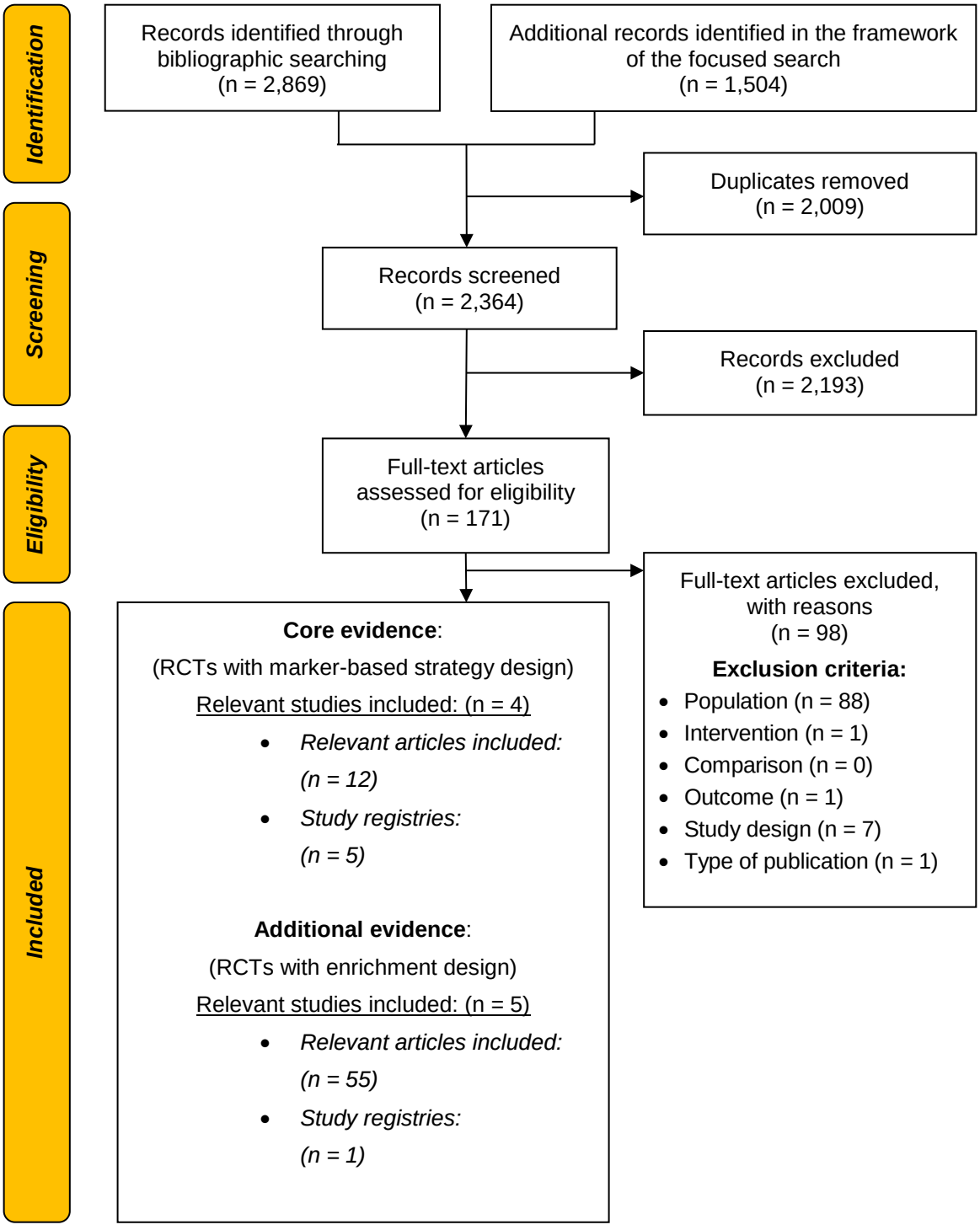

Figure 1: Flowchart of study selection

Abbreviations: RCT: randomised controlled trial, n: number

Figure 1 shows the result of the information retrieval based on the predefined inclusion criteria. References of the documents that were checked in full-texts but excluded are presented in Appendix 1 with the respective reason for exclusion.

Selection of systematic reviews and relevant studies

Selection of relevant systematic reviews (focused)

Those studies or documents identified in bibliographic databases, as well as those identified on the websites of HTA agencies, were both reviewed and assessed with regard to their relevance by 1 person from the authoring team. A second reviewer from the co-authoring team checked the whole process, including the assessment.

Selection of relevant studies and documents

- Bibliographic databases: In a 2-step procedure, the titles and abstracts of the references were first screened against the inclusion and exclusion criteria, followed by the screening of the full texts of potentially relevant publications identified in the first step,
- Study registries: In a 1-step procedure, the registry entries were screened against the inclusion and exclusion criteria.

The selection of studies retrieved from the searches in bibliographic databases and study registries was performed by 2 reviewers independently of each other (1 from the authoring team and 1 from the co-authoring team). Discrepancies were resolved by discussion.

Data management

- Endnote X8 was used for citation management.
- Study selection was performed in IQWiG's internal web-based trial selection database (webTSDB [89]).

Resulting study pool

The following tables show the resulting study pool for the present Rapid REA, divided into the core study pool containing RCTs with marker-based strategy design and the additional evidence pool containing RCTs with enrichment design.

Table 2-3: Core study pool of the Rapid REA – RCTs with marker-based strategy design

Study	Journal publication of results [reference]	Design publication [reference]	Study registry entries [reference] / Results report from study registries
Core study pool: RCTs with marker-based strategy design			
COSHIBA	Yes [18,82]	No	Yes [90] / No
ROSE	Yes [17,35,91]	Yes [84]	Yes [92] / No
SCOOP	Yes [16,93,94]	Yes [85]	Yes [95,96] / No
Yuksel 2009[a]	Yes [24]	Yes [86]	Yes [97] / No
a: due to content issues and a high loss-to-follow-up this study was only formally included. It was not considered further in the assessment. **Abbreviations:** RCT: randomised controlled trial			

Table 2-4: Additional study pool of the Rapid REA – RCTs with enrichment design

Study	Journal publication of results [reference]	Design publication [reference]	Study registry entries [reference] / Result report from study registries
Additional evidence: RCTs with enrichment design			
Chesnut 1995[a]	Yes [25]	No	No / No
FIT (Vertebral Deformity study, Clinical Fracture study)	Yes [19,20,31-34,40-81,83]	Yes [98]	No[b] / No
Liang 2017	Yes [21]	No	No[c] / No
Reid 2018	Yes [23,29]	Yes [23]	Yes [99]
Yang 2015	Yes [22]	No	No[d] / No

a: Since results on patient-relevant outcomes were not reported separately for both study arms, this study was only formally included. It was not considered further in the assessment.

b: As the study was already conducted in the 1990s, no study registry entry could be identified

c: No study registry entry could be identified. The ClinicalTrials.gov study identification number given in the publication [21] does not lead to the corresponding trial. According to the publication, the paper was funded by Novartis Pharma.

d: No study registry entry could be identified.

Abbreviations: RCT: randomised controlled trial

2.5 Data extraction and analyses

The following study characteristics and all reported results on predefined outcomes from the studies included were extracted in evidence tables by 1 reviewer from the authoring team and checked independently by 1 reviewer from the co-authoring team:

- Study characteristics (name of study, authors, year of publication, study design, intervention / control, setting / country, study duration / length of follow-up, patient-relevant outcome(s), inclusion and exclusion criteria)
- Participants / patient characteristics (number of patients / participants, age, sex, ethnic group, BMI, history of previous fractures, incidence of falls in the past year, drop-outs)
- Intervention / control characteristics (description of procedure, name and assessment of medication, concomitant therapy).

Dichotomous data were expressed as RR, HR or OR with 95 % CIs or as the number of events and percentages, continuous data were expressed as mean, SD and estimated difference of the means. All relevant data were double-checked.

Exclusion of study results

In general, results were not considered in the assessment if they were based on less than 70 % of the randomised patients, i.e. if the proportion of patients not included in the evaluation was greater than 30 % [100].

Inconsistency of results (heterogeneity)

When carrying out a meta-analysis, the existence and the extent of potential heterogeneity are statistically examined. In the event of heterogeneity, the reasons must first be investigated. These could be methodological (see section “Sensitivity analyses” below) and / or clinical (see section Subgroup characteristics and other effect modifiers” below). If unexplained heterogeneity was present, the quality of the evidence was lowered depending on the magnitude of the heterogeneity according to the GRADE approach.

Meta-analyses

If several studies are available, they should be pooled in a meta-analysis. The studies should be sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view. This should be in line with the EUnetHTA guideline "Comparators & Comparison – Direct and indirect comparisons".

The estimated effects and confidence intervals from the studies were summarised using forest plots. Subsequently, the study pool was examined for the presence of heterogeneity both visually and using statistical tests [101]. If the heterogeneity test yielded a statistically insignificant result ($p \geq 0.05$), it was assumed that estimating a common (pooled) effect usually made sense, as long as no reasons (clinical/design) existed against applying this approach. Because heterogeneity cannot be reliably estimated when only a few studies are available, fixed effect models were used in the event of 4 or fewer studies, as long as no other reasons against applying this approach existed; for instance, the studies had to be sufficiently similar. If a model with a fixed effect was not justifiable, a qualitative summary was provided. Meta-analyses were calculated with SAS, version 9.4.

If the heterogeneity test yielded a statistically significant result ($p < 0.05$), only a qualitative summary was provided.

Subgroup analyses and other effect modifiers

The results were examined with regard to potential effect modifiers, i.e. clinical factors influencing the effects. The aim was to uncover potential differences in effects between patient groups and treatment characteristics. Statistical significance based on a homogeneity or interaction test is a prerequisite for the detection of different effects. In particular, the following possible effect modifiers were to be investigated:

- sex
- age
- body weight / BMI
- ethnicity.

If further possible effect modifiers arose from the available information, these were also included, if reasonable (e.g. order of screening elements, DXA upfront versus FRAX followed by DXA) and corresponding conclusions on the effects observed were adapted, if applicable.

2.6 Quality rating

The TEC and CUR domains are based on current clinical guidelines and reviews, on input from clinical experts, and on input from other HTA agencies on the current use of the technology. For these domains, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased sources. A descriptive analysis of different information sources was performed.

The EUnetHTA guideline "Levels of Evidence – Internal validity of randomised controlled trials" was applied for the Effectiveness (EFF) and the Safety (SAF) domains. Accordingly, the risk of bias was estimated on the study and outcome level according to the following criteria: generation of randomisation sequence, allocation concealment, blinding (participants, staff, and outcome assessors), loss to follow-up, intention-to-treat analysis, and selective reporting.

In a next step, the effects were summarised (qualitatively or quantitatively depending on the existing statistical heterogeneity or content issues) at the outcome level and separately for each of the 2 RCT designs included.

To rate the quality of the overall evidence available for a given outcome, the GRADE approach was applied. In general, the quality of evidence was evaluated at the outcome level and separately for each RCT design (possible levels: high, moderate, low, very low). The following negative downgrading factors were examined. Specifically in this assessment, the quality of evidence was downgraded by 1 level if results from only 1 study were available and downgraded by 2 levels if results from only 1 subgroup of 1 small study were available (imprecision). For the enrichment design, 2 levels were regularly downgraded, which resulted in enrichment design studies being awarded a maximum of a low quality of evidence (indirectness). In addition, inconsistency and, if applicable, other factors were examined. Furthermore, positive upgrading factors were investigated according to the GRADE approach: presence of a large magnitude of an effect, dose-response gradient, or effect of plausible residual confounding (i.e. unmeasured or unknown determinants of outcome unaccounted for in the adjusted analysis are likely to be distributed unequally between intervention and control groups [36]).

If at least low-quality evidence from strategy design studies was available, the results observed in enrichment design studies were only presented as supplementary information, but were deemed too weak to affect the conclusions based on the effects observed in strategy design studies.

If only results from enrichment design studies were available, a conclusion on benefit or harm was only possible if at least low-quality evidence was available. As the quality of the evidence of enrichment design studies was downgraded due to serious indirectness, they could achieve at best a low quality of evidence, unless there was strong evidence suggesting that they should be upgraded, such as large effects. If the quality of the evidence was assessed as “very low”, no reliable conclusion on benefit or harm for the respective outcome was possible.

A summarised conclusion was made at each outcome level and jointly for the entire study pool based on the quality of the evidence assessed. The wording of the conclusions was based on the standardised wording suggested by Cochrane [102].

2.7 Patient involvement

Patients with primary osteoporosis were involved in the following way:

At the beginning of project planning, a questionnaire on the disease and its treatment was sent to 2 German patient organisations with the request that patients with primary osteoporosis complete it. The questionnaire was modified for the Rapid REA, but its basic form is well established in IQWiG's work. Three patients from the same patient organisation sent back a filled in questionnaire. The information given was used to identify and define patient-relevant outcomes. Thus, the preferences of the patients were taken into account when assessing "fractures" as the "critical outcome". This outcome was described by all 3 patients as relevant and important. No outcomes were identified by the patients that had not been assessed in the studies included and were identified as being patient-relevant when establishing the Project Plan of this Rapid REA.

Each participating patient completed a DOICU form prior to inclusion and no relevant conflict of interest was identified. Participating patients received no reimbursement. The questionnaire (English translation) can be found in Appendix 1, Section 10.1.3.

2.8 Description of the evidence used

The sub-studies of the FIT trial

The 2 sub-studies of the FIT trial, the Vertebral Deformity study [20] and Clinical Fracture study [19] were conducted and published separately after joint recruitment. As participants were randomised separately in each of the 2 sub-studies, and as the sub-studies were powered independently, they

were counted as 2 studies in this report. Nevertheless, as both study populations originate from the same basic population, data were preferred if they were available for the entire FIT population. For detailed information on the characteristics of the studies, please see Table 2-6.

Table 2-5: Marker-based strategy design RCTs: Main characteristics of the studies included

Study name [reference], year of publication	Study type	Number of postmeno-pausal women (age range)	Intervention(s)	Control	Concomitant therapy	Place and period of the study	Follow-up	Relevant (sub-) outcomes
Core study pool: Marker-based strategy design								
SCOOP, 2018 [16]	RCT	12,495 (70 to 85)	Screening for osteoporosis (informed consent, then FRAX score, then femoral neck DXA, then discussion of treatment options)	No screening	None	UK (2008 to 2014)	5 years	Osteoporosis-related fracture[a] Any clinical fracture Hip fracture[b] Mortality HrQoL
ROSE, 2018 [17]	RCT	34,229 (65 to 80)	Screening for osteoporosis (FRAX score, informed consent, then lumbar spine and hip DXA, then discussion of treatment options)	No screening	None	Denmark (2010 to 2016)	5 years	Osteoporosis-related fracture[c] Major osteoporotic fractures[d] Hip fracture
COSHIBA, 2012 [18]	RCT	3,200 (65 to 80)	Screening for osteoporosis (written consent, then clinical risk assessment, then thoracolumbar radiograph, then discussion of treatment options)	No screening	None	UK (2007 to 2010)	1 year	Any clinical fracture[e] Clinical vertebral fracture Other clinical fracture[f] Hip fracture Wrist fracture[g]

Study name [reference], year of publication	Study type	Number of postmeno-pausal women (age range)	Intervention(s)	Control	Concomitant therapy	Place and period of the study	Follow-up	Relevant (sub-) outcomes
a: operationalised as fractures “excluding the hands, feet, nose, skull, or cervical vertebrae” [16] b: operationalised as “verified fractures with a specific description of neck of femur or proximal femur. Fractures described as subtrochanteric, femoral shaft, distal femur, or simply femoral were not categorised as hip fractures” [16] c: operationalised as “all potential osteoporotic fractures, except fractures of fingers, toes, skull, or face” [17] d: operationalised as “incident clinical fractures of the hip, vertebral, wrist, and humerus” [17] e: operationalised as self-reported new fractures (forearm, hip, vertebral, other) f: operationalised as any clinical fracture other than hip, forearm, vertebral fractures g: operationalised as forearm fractures **Abbreviations:** HrQoL: health-related quality of life; RCT: randomised controlled trial; UK: United Kingdom								

Table 2-6: Enrichment design RCTs: Main characteristics of studies included

Study name [reference], year of publication	Study type	Number of postmeno-pausal women (age range)	Intervention (s)	Comparator(s)	Concomitant therapy	Place and period of the study	Follow-up	Relevant (sub-) outcomes
Additional evidence: Enrichment design								
FIT Clinical Fracture study [19]	RCT	4,432 (55 to 81)	Alendronate[a]	Placebo	Elemental calcium and vitamin D if necessary[b]	USA (1992 to 1997)	4.2 years (mean)	Any clinical fracture[c] Other clinical fracture[d] Clinical vertebral fracture Hip fracture Wrist fracture (Serious) adverse events Mortality
FIT Vertebral Deformity study [20]	RCT	2,027 (55 to 81)	Alendronate[a]	Placebo	Elemental calcium and vitamin D if necessary[b]	USA (1992 to 1996)	3 years (mean 2.9)	Any clinical fracture[c] Clinical vertebral fracture Other clinical fracture[d] Hip fracture Wrist fracture Back pain Utilisation of healthcare resources (Serious) adverse events Mortality
Liang 2017 [21]	RCT	285 (50 to 65)	Zoledronic acid[e]	Placebo	-	China[f] (2010 to 2014)	2 years	Any clinical fracture[g] Back pain (Serious) adverse events

Study name [reference], year of publication	Study type	Number of postmeno-pausal women (age range)	Intervention (s)	Comparator(s)	Concomitant therapy	Place and period of the study	Follow-up	Relevant (sub-) outcomes
Additional evidence: Enrichment design								
Reid 2018 [23]	RCT	2000 (≥ 65)	Zoledronic acid[h]	Placebo	Calcium, Vitamin D[i]	New Zealand (2009 to 2018)	6 years	Any clinical fracture[j] Clinical vertebral fracture Hip fracture Wrist or forearm fracture Serious adverse events Mortality
Yang 2015 [22]	RCT	100 (postmeno-pausal)	Zoledronic acid[k]	Placebo	Calcium, vitamin D[l]	China[m] *(no information)*	1 year	Any clinical fracture[n] Mortality

Study name [reference], year of publication	Study type	Number of postmeno-pausal women (age range)	Intervention (s)	Comparator(s)	Concomitant therapy	Place and period of the study	Follow-up	Relevant (sub-) outcomes
Additional evidence: Enrichment design								
a: alendronate sodium pills: 5 mg / d for 2 years, 10 mg/d from the third annual visit; study drug should be taken with at least 120 ml of water in a fasting state and not lie down or eat or drink any other food or liquid for at least half hour. Prescription medications that had to be taken in the fasting state could be taken before breakfast. b: daily supplement containing 500 mg of elemental calcium and 250 IU of cholecalciferol (vitamin D), if dietary calcium intakes were less than 1,000 mg / d c: defined as any clinical fracture (including non-spine and clinical vertebral fractures) d: defined as fractures of the shoulder, arm, hand, fingers, ribs, chest, pelvis, coccyx, sacrum, leg, ankle, foot, toes, peri-prosthetic fractures) e: 5 mg/year intravenous zoledronic acid, administered as a 15-min to 30-min intravenous infusion f: Xinhua Hospital in Zhejiang, East China g: operationalised as “fragility fractures” h: 4 infusions of 5 mg zoledronate at 18-month intervals i: women who were not already taking vitamin D supplements were given a single oral dose of cholecalciferol (2.5 mg [100,000 IU]) at least 1 week before their first infusion and subsequently received cholecalciferol at a dose of 1.25 mg per month for the duration of the trial. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not supplied. j: operationalised as “symptomatic fragility fracture”: included symptomatic vertebral fractures and all nonvertebral fractures m: operationalised as any non-vertebral fragility fracture and excluded fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible as well as pathological fractures k: 5 mg infusion zoledronic acid (Novartis Pharma Schweiz AG, Switzerland) l: supplementation of 1,000 mg of Calcium and 400 IU of vitamin D daily m: It is assumed that the study was conducted in China. There is no specific information in the publication of the study. n: operationalised as “fractures” **Abbreviations**: d: day; IU: international unit; mg: milligrams; ml: millilitres; RCT: randomised clinical trial; USA: United States of America								

For detailed information on in- and exclusion criteria, characteristics of the population and the intervention of included studies please see Tables A-2 to A-7 in Appendix 1.

2.9 Deviations from the Project Plan

In addition to the 2 study registries ClinicalTrials.gov (U.S. National Institutes of Health) and International Clinical Trials Registry Platform Search Portal (World Health Organisation) listed in the Project Plan, an additional search was conducted in the EU Clinical Trials Register (European Medicines Agency).

The use of strontium ranelate is limited by EMA and the production of the drug has been stopped. Since strontium ranelate is no longer recommended by the current European Guideline on osteoporosis in postmenopausal women [1], this drug was removed from the list of anti-osteoporosis drug treatments (see Section 2.3 in this Rapid REA, Table 2-3 in the Project Plan).

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is screening for osteoporosis? What procedure elements are included in the entire screening and treatment process?
B0002	What is the claimed benefit of screening for osteoporosis in relation to no screening in the general population?
B0003	What is the phase of development and implementation of screening in the general population?
B0004	Who administers the different parts of the screening and treatment process for osteoporosis? In what kind of care settings is it used (e.g. GP practices)?
B0009	What equipment and supplies are needed to screen for osteoporosis?
A0020	For which indications have each of the potential technical devices and pharmaceuticals received marketing authorisation or CE-marking?
A0021	What is the reimbursement status of the technology?

3.2 Results

3.2.1 Features of the technology and comparators

[B0001] – What is screening for osteoporosis? What procedure elements are included in the entire screening and treatment process?

Patients with osteoporosis can be identified either via organised screening or opportunistically by case finding [1]. However, there is currently no agreed policy for osteoporosis screening in Europe [1]. In the context of this Rapid REA, population-based screening using a clinical risk assessment tool and / or BMD measurement (DXA, qUS, qCT) was evaluated. The exact implications of a general case-finding strategy vary internationally depending on the cut-offs defined in the various countries, their recommendations on measuring BMD in addition to the assessment of clinical risk factors, and the availability of DXA [1].

According to European guidelines by the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and International Osteoporosis Foundation (IOF), several factors besides a low BMD increase the risk of fractures [1] (see [A0003]). In addition to sex, age and BMI, these include a family predisposition and lifestyle (physical exercise, diet, smoking and alcohol habits) and causes for secondary osteoporosis such as rheumatoid arthritis [1].

Risk assessment tools

Risk assessment tools that can be used either on their own or in conjunction with BMD measurements have been developed, as BMD measurement alone fails to identify many patients at a high risk of fracture [1,3]. The risk assessment tools are used to make decisions regarding further diagnostic work-up of patients and / or to directly make a decision regarding their eligibility for treatment [1,2,4].

A recent SR of risk assessment tools identified 48 different tools for predicting either BMD or fractures [2]. They differ in their complexity and include between 1 and 31 risk factors, although “none

of the tools performed consistently better than the others and simple tools (…) often did as well or better than more complex tools (…)" [103]. All the fracture-predicting tools included age, while the 4 most frequently included factors were weight, prior fracture, BMD, and maternal or parental history of fracture [103]. Less than half of all risk assessment tools were externally validated. The 3 fracture-predicting tools that were most frequently externally validated are described below.

The risk assessment tool most commonly used in clinical guidelines is the FRAX tool [2]. The FRAX tool is a computer-based algorithm to assess the risk of fractures and was developed at the University of Sheffield with grants from industry and from publicly funded organisations [4,104]. The tool was also sometimes mistakenly called the World Health Organisation (WHO) tool [105]. The WHO has therefore clarified that it "has no access to the algorithms, coefficients or underlying data on which the FRAX tool and its national variations have been developed. Consequently WHO is unable to, and does not, express any opinion regarding the scientific value of the FRAX® tool. It should be clear that any treatment recommendations integrated with the FRAX® tool have not been evaluated by the WHO's Guidelines Review Committee and should not be construed as WHO-endorsed recommendations" [105].

The aim of the FRAX tool is to identify patients with risk factors for a reversible risk of fracture, i.e. a risk of fracture that responds to treatments that change bone mass and strength [4]. FRAX is used to calculate the 10-year probability of a major fracture or the 10-year probability of a hip fracture [1]. According to the current guideline of the German-speaking scientific societies on osteology (DVO) the performance of the FRAX-tool in this regard varies and has not proven to be superior to a DXA-based approach [10].

FRAX assesses the following factors: age, sex, low body mass index, previous fragility fracture, parental history of hip fracture, glucocorticoid treatment, current smoking, and alcohol intake [1]. FRAX also considers causes of secondary osteoporosis such as rheumatoid arthritis, untreated hypogonadism in men and women, inflammatory bowel disease, prolonged immobility, organ transplantation, type 1 and type 2 diabetes, thyroid disorders, chronic obstructive pulmonary disease, and HIV infection [1]. The risk based on FRAX can be assessed either with or without BMD.

However, many conditions are considered only by means of the rather general risk factor "secondary osteoporosis" [1] and the consensus paper by the Belgian Bone Club raised concerns that FRAX may, for example, underestimate fracture risks in frail individuals, including those with the following risk factors: anorexia nervosa, cancer, sarcopenia, dialysis, and very old age [106]. Another risk factor not explicitly included in FRAX is the risk of falls, "since the risk of fracture that is identified may not be associated with reversibility of risk" [1].

Especially in older populations, the long-term probability of fractures may be underestimated if death is not accounted for as a competing risk [107]. The FRAX tool considers death as a competing risk [1]. The hazards for death and for fractures can vary markedly between countries and ethnicities, and therefore the use of country-specific FRAX tools is recommended [1,2,4].

By 2018, FRAX models for 64 countries had been developed [4]. Despite these efforts, the quality of these models is likely to vary significantly due to the quality of the underlying data [2]. The rates of hip fractures within the same country, but particularly between countries, can vary up to a factor of 2 for the former and a factor of 15 for the latter, without any clearly identifiable causes [2]. The FRAX tool has been mostly validated in Caucasian populations [2] and those risk estimates may not be applicable to other populations [2,4,107]. Some countries, e.g. the USA and China, therefore have ethnic-specific FRAX models [2].

The **Garvan** fracture risk calculator was developed on the basis of an Australian population and validated in Australia, New Zealand, and Canada. It includes an assessment of the following risk factors: age, sex, fractures after age of 50 years (none, 1, 2, ≥ 3), history of falls in the previous 12 months (none, 1, 2, ≥ 3), plus either BMD or weight [2,5,108]. It estimates the 5-year or 10-year risk of any osteoporotic fracture (hip, clinical vertebrae, wrist, metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, or sternum) and the 5-year or 10-year risk of hip fracture [5].

The **QFracture-Score-2016** was developed on the basis of populations from 357 general practices in England and Wales [5]. The following risk factors are used in the score: age, sex, height, weight, smoking, alcohol, diabetes, previous fracture, parenteral osteoporosis or hip fracture, living in a nursing home or care home, history of falls, dementia, cancer, asthma or chronic obstructive pulmonary disease (COPD), cardiovascular disease, chronic liver disease, advanced chronic kidney disease, Parkinson's disease, rheumatoid arthritis, systematic lupus erythematosus, malabsorption, endocrine problems, epilepsy or anticonvulsant use, antidepressant use, steroid use, and hormone replacement therapy [5]. It estimates the 1- to 10-year risk of any fracture (hip, vertebral, proximal humerus, or distal radius) and of hip fracture and has been validated in the UK and in Ireland [2].

While the Garvan tool incorporates dose response into its algorithm for previous fractures, falls, and QFracture for smoking, alcohol intake, and type of diabetes, the FRAX tool does not [2]. However, there is the option to make subsequent adjustments to the FRAX risk based on the degree of exposure to glucocorticoids, BMD results for the lumbar spine, trabecular bone score, hip axis length, falls history, immigration status, and type 2 diabetes [1].

BMD testing

Depending on the approaches defined in the guidelines, BMD measurement is part of the management strategy or not. It can be performed on different parts of the body and with a variety of techniques. The most established method for measuring BMD is DXA [12].

In DXA, 2 x-ray beams with different energy levels are aimed at the hip, lumbar spine, or forearm. After subtraction of soft tissue absorption, the BMD can be determined from the absorption of each beam by the bone [12]. The measurements made are compared with those of young healthy adults in order to determine by how much they deviate [1]. If measurements at the hip or spine deviate by 2.5 SDs or more below those of a healthy young adult (T-score ≤ -2.5), the criteria for an operational diagnosis of osteoporosis are fulfilled [1,104,109].

Other techniques used to determine BMD are qCT and qUS. The former generates a cross section image in which tissue density for specific areas can be determined [12]. For the hip, BMD values that correspond to the T-scores measured with DXA can be derived from qCT measurements by computed tomography x-ray absorptiometry (CTXA) [10]. At the spine, cortical endplate bone strongly contributes to the BMD measured via DXA, while qCT remains unaffected, as it only measures cancellous bone [12]. The T-scores derived for BMD based on DXA cannot be applied to qCT [12]. In particular, qCT is more sensitive to change than DXA, as cancellous bone changes at a higher rate than cortical bone [12]. Nevertheless, in patients with degenerative changes of the spine, qCT can be an alternative to DXA [12]. The latter may be inappropriate in these patients as it can yield BMD measurements that are misleadingly high [12]. While qCT is highly accurate for BMD measured in the pre-specified area, the exposure to radiation is much higher than with DXA [12].

Quantitative US examines the bone at the heel of the foot (calcaneus) and is based on the measurement of the differential absorption of sound waves rather than x-ray beams [12]. The ACR guideline states that while osteoporotic bone shows lower velocities, the measurements do not measure BMD and it is therefore not possible to apply the WHO definition for osteoporosis [12].

Another and newer technique is the trabecular bone score (TBS), which further analyses DXA images of the lumbar spine [1] in order "to describe the skeletal microarchitecture" [12]. It measures "relative pixel amplitude variations summing the squared gray level differences" and like the other techniques provides information on bone quality instead of bone quantity [12]. As TBS predicts fracture risk independently of FRAX, possible adjustments to the FRAX-score based on TBS results have been developed [1].

Treatment

Osteoporosis treatment has mostly been investigated in women; insufficient evidence is available for the treatment of men [12]. Most of the evidence for treating osteoporotic men originates from trials with mixed populations [12].

General measures

General measures recommended by the European guideline aim at reducing the risk of falls and fractures by reviewing the medication for any drugs that can affect BMD and/or the risk of falls, as well as assessing and correcting visual acuity, adapting the home environment and further measures [1]. The USPTF guidance on osteoporosis refers to its guidance for "Interventions to Prevent Falls in Community-Dwelling Older Adults", where they recommend to selectively offer multifactorial interventions to community-dwelling adults who are 65 years old or older and at an increased risk of falls, depending on individual circumstances (benefit and harm) and preferences [8,11].

Hip protectors may slightly reduce the risk of fractures close to the hip; compliance and adherence to their use is poor, thereby limiting their benefit [1,10]. However, according to the European guideline the available evidence seems to be contradictory [1].

Physical activity

The American College of Physicians (ACP) guideline of 2017 concluded that "evidence is insufficient to conclusively show the effect of physical activity on fracture risk" [9]. The USPTF guidance on osteoporosis refers to its guidance for "Interventions to Prevent Falls in Community-Dwelling Older Adults" where they recommend exercise interventions for community-dwelling adults who are 65 years old or older and at an increased risk of falls [8,11].

The ESCEO guideline stresses the importance of weight-bearing exercise as part of the management of osteoporosis and states that fall prevention exercise reduces the risk of falls associated with injuries and fractures [1]. The DVO guideline recommends that regular exercise should be encouraged with the aim of improving muscle strength, balance, and coordination [10].

Drug treatment and supplements

Table 3-1 gives an overview of the different classes of drugs used for the treatment of osteoporosis. The ACP guideline states that the evidence is insufficient to recommend one treatment over the other, as direct comparisons of the interventions are lacking [12]. According to the DVO guideline, the osteoporosis treatment should be reviewed every 3 to 5 years [10].

Calcium and vitamin D

In clinical studies, most anti-osteoporosis drugs have been used in conjunction with calcium and vitamin D, so that evidence on drug treatment of osteoporosis without such supplementation is

lacking [110]. According to the ACP and DVO guidelines, the effect of calcium and vitamin D on fracture risk seems to be uncertain [10,12]. An Italian guideline reported that vitamin D supplementation has modest effects on BMD at the hip that are proportional to the severity of the deficiency and that effects on fracture risks are due to a reduction in falls [111]. On the other hand, studies where patients received high vitamin D dosages per year have reported a high risk of hip fracture [1].

The DVO guideline recommends ensuring an adequate intake of at least 1000 mg of calcium per day and a sufficient supply of vitamin D, in particular before treatment with parenteral antiresorptive medication [10]. Several guidelines suggest that vitamin D and calcium should be supplemented if patients are deficient or if sufficient oral intake within a normal diet is uncertain [10]. The isolated supplementation of vitamin D is not being recommended [8,10].

Bisphosphonates

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone [112]. They inhibit bone resorption by reducing the number and activity of the osteoclasts [1].

Contraindications for the use of bisphosphonates are abnormalities of the oesophagus and other factors that delay oesophageal emptying such as stricture or achalasia, inability to stand upright for at least 30 minutes or hypocalcaemia [113,114]

RANK ligand inhibitor

Denosumab is a human monoclonal antibody against the ligand of the receptor activator of nuclear factor NFkB (RANKL) [1,115] and by binding to RANKL acts on the osteoclasts via the RANK receptor [1]. Hypocalcaemia is a contraindication for denosumab [116].

If treatment with denosumab is stopped or discontinued, it is necessary to start an alternative treatment, as patients were then found to have a similar rate of vertebral fractures to patients who had been on placebo and then discontinued it [1,10]. One option would be treatment with bisphosphonates [1].

Peptides of the parathyroid hormone family

Parathyroid hormone and teriparatide act on the osteoblasts [1,117]. The osteoblasts in turn improve skeletal architecture and increase bone mass [1].

The marketing authorisation for parathyroid hormone for the treatment of osteoporosis was withdrawn at the request of the marketing authorisation holder [1,118].

Contraindications for teriparatide are hypersensitivity to the active substance or to any of the excipients, pregnancy and breast-feeding, pre-existing hypercalcaemia, severe renal impairment, metabolic bone disease other than primary osteoporosis or glucocorticoid-induced osteoporosis, unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, skeletal malignancies, or bone metastases [117,119].

Treatment with teriparatide is limited to 24 months [10,117]. The ESCEO guideline recommends treatment with teriparatide in patients with high fracture risks, in particular if they have vertebral fractures [1].

Selective oestrogen receptor modulators (SERMs)

Depending on the organ, SERMs act either as an oestrogen agonist or antagonist – raloxifene and bazedoxifene have an antagonistic effect on the bone [120]. Raloxifene also reduces the risk of invasive breast cancer [1,10].

Raloxifene is contraindicated in patients with hypersensitivity to the active substance or to any of its excipients, child-bearing potential, active or past history of venous thromboembolic events, hepatic impairment including cholestasis, severe renal impairment, unexpected uterine bleeding, as well as signs or symptoms of endometrial cancer [121].

Bazedoxifene is contraindicated in patients with a history of venous thromboembolism, undiagnosed uterine bleeding or signs of endometrial cancer or in women of child-bearing potential [122].

Dual-acting bone agent (strontium ranelate)

The production of the drug was stopped by Servier because of insufficient demand due to potential adverse effects (severe hypersensitivity reactions and cardiovascular adverse effects [123-125]).

Duration of therapy

It seems unclear for how long anti-osteoporosis treatment should be given. According to a recent report for the AHRQ “only alendronate, zoledronate, and oral hormone therapy reduced nonvertebral fractures with long-term treatment. (...) While fracture benefits of continued osteoporosis drug treatment versus drug holiday numerically appeared to outweigh these risks, the more limited morbidity prevented and greater uncertainty about the outcome measures and risk estimates require further investigation to better inform clinical decisions about continuing treatment” [126].

Combination therapy

While first studies showed that BMD measurements improve with combination therapy compared with monotherapy, e.g. concomitant treatment with teriparatide and denosumab, the DVO guideline does not recommend combination therapy, as no data on fracture incidence are available yet, but states that it can be considered as an option in individual cases [10].

Table 3-1: Summary of the evidence on drug treatments for low BMD and osteoporosis adapted from the guideline of the American College of Physicians [9]*

Treatment	Effect on fracture risk in osteoporotic women and evidence quality			Efficacy in male osteoporosis	Adverse events and evidence quality
	Vertebral	Non-vertebral	Hip		
Bisphosphonates	Summarised individually below	Summarised individually below	Summarised individually below	Summarised individually below	As a class: atypical subtrochanteric fracture, osteonecrosis of the jaw (low quality)
Alendronate	Improves; high quality	Improves; high quality	Improves; high quality	Yes [127]	Mild upper GI symptoms (high quality)
Ibandronate	Improves; high quality	Uncertain[a]	Uncertain[a]	No [127]	Mild upper GI symptoms (high quality); myalgias, cramps and limb pain
Risendronate	Improves; high quality	Improves; high quality	Improves; high quality	Yes [127]	Mild upper GI symptoms (high quality)
Zoledronic acid	Improves; high quality Improves in osteoporotic men; moderate quality	Improves; high quality	Improves; high quality	Yes [127]	Mild upper GI symptoms; hypocalcaemia, influenza-like symptoms (high quality); atrial fibrillation; arthritis and arthralgias, headaches, uveitis
RANK ligand inhibitor					
Denosumab	Improves; high quality	Improves; high quality	Improves; high quality	Yes [127]	Mild upper GI symptoms (high quality), infection (moderate quality); rash

Treatment	Effect on fracture risk in osteoporotic women and evidence quality			Efficacy in male osteoporosis	Adverse events and evidence quality
	Vertebral	Non-vertebral	Hip		
Peptides of the parathyroid hormone family					
PTH	Improves in women with prior vertebral fracture [128]	No evidence available [128]	-	-	Very common: hypercalcaemia, hypercalciuria, nausea, common: dizziness, headache, blood calcium increased, palpitations, vomiting, constipation, dyspepsia, diarrhoea, muscle cramp, pain in extremity, back pain, urine calcium / creatinine ratio increased, urine calcium increased, injection site erythema, fatigue, asthenia
Teriparatide	Improves; high quality	Improves; high quality	Unknown	Yes [127]	Mild upper GI symptoms, headache, hypercalcaemia (high quality), hypercalciuria, renal adverse effects
Selective oestrogen receptor modulators (SERMs)					Common; vasomotoric symptoms, muscle cramps; uncommon: venous thrombosis. Contraindications and important warnings: venous thromboembolism, pregnancy [5]
Raloxifene	Improves; high quality	No effect	No effect	No [127]	Hot flushes[b], thromboembolic events (high quality); pulmonary embolism, cerebrovascular death
Bazedoxifene	Improves [5]	No effect [5][d]	Not determined [5][d]	-	See SERMs [5]

Treatment	Effect on fracture risk in osteoporotic women and evidence quality			Efficacy in male osteoporosis	Adverse events and evidence quality
	Vertebral	Non-vertebral	Hip		
Dual-acting bone agent					
Strontium ranelate [127]	Improves [127]	Improves [127]	Improves [127]	Yes [127]	Use limited by EMA due to possible thromboembolic complications and increased risk of cardiovascular diseases [127]. Risk of severe hypersensitivity reactions: drug rash with eosinophilia and systemic symptoms (DRESS) [129]
Calcium and vitamin D					
Calcium and vitamin D	Uncertain	Uncertain	Uncertain		Increased risk of hypercalcaemia
Menopausal hormone therapy					
Menopausal hormone therapy	No improvement in post-menopausal women with established osteoporosis; moderate quality Improves in postmenopausal women (not selected for having osteoporosis) (high quality)	Uncertain[c]	Improves in postmenopausal women (not selected for having osteoporosis) (high quality)	NA	Increased risk of cerebrovascular accidents and thromboembolic events (high quality)

Treatment	Effect on fracture risk in osteoporotic women and evidence quality			Efficacy in male osteo-porosis	Adverse events and evidence quality
	Vertebral	Non-vertebral	Hip		
*Unless specified otherwise, information is from the table of the ACP guideline [12] - no information provided a: According to the ESCEO guideline, it is effective in subsets of patients only based on post-hoc analysis [1]. b: “Flashes” in original publication but probably typo (based on NICE technology appraisal) [130] c: According to the ESCEO guideline, it also reduces the risk of non-vertebral fractures (including hips) [1]. d: According to the ESCEO guideline, effects are supposed to be similar to those of alendronate, ibandronate, and risendronate for both vertebral and non-vertebral fractures [1]. **Abbreviations:** EMA: European Medicine Agency; GI: gastrointestinal; NA: not applicable; NF: nuclear factor; PTH: parathyroid hormone; RANK: receptor activator of NF-κB; SERMs: selective oestrogen modulators					

[B0002] – What is the claimed benefit of screening for osteoporosis in relation to no screening in the general population?

Screening for osteoporosis may help to initiate preventive measures before osteoporotic fractures occur. While osteoporotic fractures – in particular of the spine – can be asymptomatic, they are overall associated with significant morbidity and mortality [12].

[A0021] – What is the reimbursement status of the technology / comparator? and

[B0003] – What is the phase of development and implementation of screening in the general population?

According to a survey answered by 19 EUnetHTA partners from 15 countries partners, none currently offers screening in the general population. However, Poland is currently planning a national screening programme for osteoporosis, which is due to be launched in 2023. Women aged 50 to 70 years will be eligible for screening with FRAX, DXA and X-ray. In addition to screening, this programme will include education for physicians and patients. The survey is presented in Table A-29 in Appendix 2: REGULATORY AND REIMBURSEMENT STATUS.

In Norway, screening of healthy women is being offered by private / commercial health care, and sometimes also by physicians in public health care, although it is unclear how common this is; there is no official public screening programme. In Romania, screening for the general population is only offered by private companies or research centres.

In Spain, opportunistic screening in primary care is being recommended based on a consensus paper by the Spanish Ministry of Health in people aged 70 years or older. This consensus paper also recommends that frail patients or patients at risk of falling should be actively identified within the context of already existing programmes for chronic patients and the elderly.

In Slovenia, patients at risk are being identified within the context of a FRAX programme in primary health care funded publicly and supported by the FRAX programme. A screening programme in the general population does not exist.

In several countries (Hungary, Slovenia, Germany, Norway, Denmark, Spain, Ireland, Switzerland) case-finding strategies based on risk factors or the suspected presence of secondary osteoporosis are being offered. In 3 countries (Germany, Denmark, Ireland), the presence of fractures was reported as an indication for further investigations. In Ireland, besides low trauma fracture, osteopenia in an x-ray, use of corticosteroids (i.e. prednisolone for three months or more), family history of osteoporosis (especially maternal hip fracture), and other clinical risk factors, such as loss of height, kyphosis, low BMI (<19 kg / m2), and the possibility of secondary osteoporosis, were listed as risk factors for targeted high-risk assessments. In Germany, Denmark, Spain, Switzerland and Ireland, DXA testing is offered to patients at risk. In Germany and Switzerland, follow-up testing with DXA is usually only reimbursed 5 years after the initial testing, but may be offered earlier, depending on specific indications based on treatment-relevant medical history and clinical findings. In Switzerland, follow-up testing is reimbursed every 2 years as long as risk factors are still present. In Denmark, a fracture liaison service is offered in some hospitals.

Romania performs “passive screening” with DXA. For details on this programme, please see Table A-29 in Appendix 2: REGULATORY AND REIMBURSEMENT STATUS.

[B0004] – Who administers the different parts of the screening and treatment process for osteoporosis? In what kind of care settings is it used (e.g. GP practices)?

As screening for osteoporosis in the general population has not yet been widely implemented, little experience regarding the organisation of such a service exists. In the clinical trials identified, the personnel assessing the risk factors varied. In the Danish ROSE trial, the FRAX score was derived

on the basis of a self-administered questionnaire sent out to the population, while in a Canadian trial patients were recruited through newspaper adverts; pharmacists in the community then assessed risk factors and, depending on the scoring, recommended that the patients should see a physician for further assessment [17,24]. In the SCOOP trial, screening took place in primary care [16].

[B0009] – What equipment and supplies are needed to screen for osteoporosis?

The European guideline from 2019 suggests different case-finding strategies depending on the availability of DXA in a country [1] (see [B0001]). About 11 DXA units per million of the general population are necessary in order to perform DXA testing for any women with clinical risk factors for fractures; this number of DXAs needed is probably increasing due to demographic changes [1]. EU countries that fall into this category are Belgium, Greece, France, Austria, Slovenia, Portugal, Cyprus, Germany, Italy, Finland, Denmark, Slovakia, and the Netherlands [1]. However, the need for DXA will very much depend on the role DXA is to play in the management of osteoporosis in each country.

Treatment options are outlined under research question [B0001]. The amount of supplies needed here will depend on how the indication for treatment is defined. The USA, for example, have defined a fracture risk of 3 % for hip fracture and 20 % for major osteoporotic fractures (MOF) as the intervention threshold, which was chosen based on cost-effectiveness criteria [1]. This cut-off has been adopted in guidelines by many other countries, even though it cannot be assumed that the estimates on cost-effectiveness can simply be transferred from the USA [1].

[A0020] – For which indications have each of the potential technical devices and pharmaceuticals received marketing authorisation or CE-marking?

Guidelines recommend that the decision for further diagnostic work-up and/or treatment should be based on the identification of risk factors for osteoporosis such as age and glucocorticoid treatment [1,8,10,107]. The risk assessment tools suggested for such tasks would be subject to neither marketing authorisation nor Communauté Européenne (CE) marking. The evaluation and comparison of the effectiveness of the large number of devices (in particular DXA) and drugs for diagnosing and treating low BMD, which may be part of the subsequent management after the initial risk assessment, is not the primary objective of this Rapid REA.

Even though the subsequent management of low BMD will affect the effectiveness of any screening, the decision was made that a comprehensive review of the CE status and marketing authorisation of all of the drugs and devices currently available for the diagnosis and treatment of patients with osteoporosis would be very time consuming and of very limited practical use. Such a review was therefore not undertaken.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is osteoporosis?
A0003	What are the known risk factors for osteoporosis?
A0004	What is the natural course of osteoporosis?
A0005	What are the symptoms and the burden of osteoporosis for the patient?
A0024	How is osteoporosis currently diagnosed according to published guidelines and in practice?
A0025	How is osteoporosis currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population in the different European countries? Are there differences in the epidemiology?
A0011	How much is screening for osteoporosis practiced in Europe to guide pharmacological management and fracture prophylaxis?

4.2 Results

4.2.1 Overview of the disease or health condition

[A0002] – What is osteoporosis?

Osteoporosis is defined as “a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [5,6]. It needs to be distinguished from osteomalacia, which is caused by a lack of bone mineralisation and where the ratio between mineralised and non-mineralised bone is affected [131].

According to the WHO definition from 1994, osteoporosis is diagnosed if the BMD lies 2.5 SDs or more below than that of a healthy young adult; this is called the T-score [1,5,131]. On the basis of this definition, a WHO analysis from 1985 estimated that about 30 % of all post-menopausal women in England and Wales had osteoporosis, of which 15 % had suffered a prior fracture of the proximal femur, pelvis, spine, distal forearm, or proximal humerus [131]. In contrast, using the same definition, an ESCEO analysis from 2010 estimated that 21 % of the 50- to 84-year-old women in the EU had osteoporosis [1].

Although diagnosis of the disease relies on the quantitative assessment of BMD, the patient-relevant significance lies in the fractures that may occur as a consequence of decreasing bone density. The individual fracture risk does not arise from a low BMD alone; non-skeletal factors (e.g. age, frailty, family history) also have to be considered. Therefore, in this Rapid REA, osteoporosis is not only understood as the arbitrary definition of low BMD, but as the individual fracture risk to which BMD contributes as an important factor.

Secondary osteoporosis develops due to other diseases (e.g. rheumatoid arthritis) or their treatment (e.g. corticosteroids). While these patients would not be formally excluded in a screening pro-

gramme for the general population, ideally any treatment needs for osteoporosis should be identified as part of the routine care for their underlying condition. The focus of a screening programme in the general population is hence upon in the identification of patients with primary osteoporosis.

Epidemiology

According to a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA), about 27.6 million people in the EU27 (22 million women and 5.6 million men) aged 50-84 years in 2010 had osteoporosis as defined by the WHO criteria[3] [1,7]. It was estimated that these numbers will increase to 33.9 million in 2025 for the whole population in the EU due to demographic changes [7,132]. The prevalence of osteoporosis ranged from 3.7 % for Ireland and Cyprus to 6.3 % in Italy for the total population [7]. For women aged 50 years or older, the prevalence ranged from 19.3 % in Cyprus to 23.4 % in Italy; for men aged 50 years or older, the prevalence ranged from 5.7 % in Slovakia to 6.9 % in Greece, Italy, and Sweden [7].

The prevalence of osteoporosis increases with age [7]. For the EU27 it was estimated that in 2010 the prevalence increased from 6.3 % (women) and 2.5 % (men) in persons aged 50 to 54 years to 47.2 % (women) and 16.6 % (men) in persons aged 80 years or older [7]. When the population was divided into 5-year age groups, the absolute number of women with osteoporosis per age group also gradually increased until the age group of 80 years and more (3,876,000 in the 75-79 year group and 7,350,000 in the 80 years and more group) [7]. For men, the highest number with osteoporosis was also found in the open-ended age group of 80 years or more, but if only the 5-year age groups were considered, then the largest number of men with osteoporosis was estimated to be in the 60 to 64 year group (826,000 men) [7]. The total number of people aged 50 years or more estimated to be at risk of developing osteoporosis in 2010 was 99,906,000 women and 83,491,000 men [7].

The estimated number of new fractures in the EU in 2010 was approximately 3.5 million, with about two thirds occurring in women [7]. Of these, about 620,000 affected the hip, 520,000 the vertebrae, 560,000 the forearm, and 1.8 million other locations [7]. For Switzerland, the incidence of MOF was estimated to be 2,078 per 100,000 for women and 773 per 100,000 for men aged 50 years or more based on data from 2000 and 2006 [10]. The estimated lifetime risk of MOF in Switzerland was 51.3 % for women and 20.2 % for men aged 50 years [10].

More recent data for 6 European countries (France, Germany, Italy, Spain, Sweden, and UK) are presented in Table 4-1. Differences in BMD do not explain the differences in fracture risk between the countries and it is unclear why they differ [133]. Potential reasons for the differences observed include differences in body mass index, calcium intake, degree of sunlight exposure, and socio-economic prosperity [133].

About 43,000 deaths in the EU were related to fractures in 2010 [7]. Of the fracture-related deaths in women, 50 % were due to hip fractures, 28 % to clinical vertebral fractures, and 22 % due to other fractures; in men, 47 % were due to hip fractures, 39 % to clinical vertebral fractures, and 14 % to other fractures [7].

[3] Numbers given for men in the primary source differ slightly between the main text (5.6 million) versus the abstract and the ESCEO guideline (5.5 million men). As one of the authors of the ESCEO guideline is a co-author of the primary study, it is assumed that the latter number is correct.

Table 4-1: EU6 data for 2015/2017 adapted from the website of the International Osteoporosis Foundation [132]

		EU6	France	Germany	Italy	Spain	Sweden	UK
Estimated number of individuals aged 50+ with osteoporosis in 2015		20 million	3.8 million	5.3 million	4 million	2.8 million	500,000	3.5 million
Prevalence of osteoporosis aged 50+ in 2015[a]	**Men**	Not available	6.9 %	6.7 %	7.0 %	6.8 %	6.9 %	6.8 %
	Women		22.7 %	22.5 %	23.1 %	22.5 %	22.5 %	21.8 %
Estimated life time risk of hip fracture aged 50	**Men**	6.1 to 13.7 %	6.0 %	9.8 %	7.9 %	9.0 %	13.7 %	8.3 %
	Women	9.8 % to 22.8 %	11.0 %	17.1 %	16.7 %	10.0 %	22.8 %	17.2 %
Estimated life time risk of MOF fracture aged 50	**Men**	18 %	13 % [134]	20 % [135]	16 % [136]	18 % [137]	29 % [138]	17 % [133]
	Women	31 %	22 % [134]	35 % [135]	34 % [136]	20 % [137]	46 % [138]	35 % [133]
Incidence of fragility fractures per year in 2017		2.7 million	382,000	765,000	563,000	330,000	120,000	520,000
Estimated increase in fragility fractures 2017 - 2030		+23.0 %	+24.4 %	+18.5 %	+22.4 %	+28.8 %	+26.6 %	+26.2 %
Hours of care[b] after a hip fracture per 1000 individuals, per year		370 h	138 h	Not available	882 h	756 h	191 h	248 h

a: not age-standardised
b: care provided by relatives
Abbreviations: EU6: 6 selected European countries (France, Germany, Italy, Spain, Sweden, UK); h: hours; MOF: major osteoporotic fractures; UK: United Kingdom

[A0003] – What are the known risk factors for osteoporosis?

Risk factors for osteoporosis include age, sex, low BMI, previous fragility fracture, parental history of hip fracture, current smoking, and alcohol intake [1]. Causes of secondary osteoporosis include glucocorticoid treatment, rheumatoid arthritis, untreated hypogonadism in men and women, inflammatory bowel disease, prolonged immobility, organ transplantation, type 1 and type 2 diabetes, thyroid disorders, chronic obstructive pulmonary disease, and HIV infection [1] (see also [B0001]). The prevalence of primary osteoporosis differs by race / ethnicity [14].

[A0004] – What is the natural course of osteoporosis?

While osteoporotic fractures – in particular of the spine - can be asymptomatic, they are overall associated with significant morbidity and mortality [12]. According to the European guideline, the risk of fracture of the hip, spine, forearm, or proximal humerus is about 45 % within the next 10 years for women with osteoporosis [1]. For “each SD decrease” of the BMD, the fracture risk is estimated to increase by a factor of 1.5 to 3.0, although this varies depending on the device used and the site assessed [1] (see also questions [A0005] and part II of [A0023]). The risk of falling increases with age and frailty. Frailty and osteoporosis are associated with each other, as they share several risk factors [139]. Järvinen 2015 estimate that the effect of age on hip fracture risk is about 11 times higher than the effect of risk of reduced BMD [140].

4.2.2 Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of osteoporosis for the patient?

Osteoporosis per se is asymptomatic but is, among other things, a risk factor for fractures, which are associated with significant morbidity and mortality and decreased quality of life [10,12]. Osteoporotic fractures cause acute and chronic pain, gastro-oesophageal reflux, limited body function, and can lead to hospitalisation and admissions to nursing homes [10].

Every fourth patient who is still working and diagnosed with osteoporosis has to either “give up work, change the job or reduce [his or her] hours” according to the IOF report for the UK [133].

Depending on the location of the fracture, patients may need hospitalisation, which is nearly always needed in the case of hip fractures [107]. The NICE guideline estimated that half the patients with a hip fracture will be permanently disabled and that only 30 % of the patients with hip fracture will fully recover [107]. The proportion of patients requiring long-term care after hip fracture in Europe rises from 2.1 % for those aged 50 to 60 years to 35.3 % for those aged 90 years or older [133].

The risk of dying is highest around the time of a fracture, e.g. most deaths due to hip fractures occur within 3 to 6 months; the risk then gradually decreases, although it never reaches the levels of the general population [1,7]. In the NICE guideline, the risk of dying after hip fracture was estimated to be 20 % [107]. For 2010, the risk of dying in the first year after a fracture was estimated as 23 per 100,000 for women and 24 per 100,000 for men in the EU27 [7]. According to the USPTF between 21 % and 30 % of patients die within the first year after a hip fracture [8].

4.2.3 Current clinical management of the disease or health condition

[A0024] – How is osteoporosis currently diagnosed according to published guidelines and in practice?

According to the survey performed in the course of this assessment among HTA agencies involved in EUnetHTA (see Appendix 2) and a review of the most recent European guidelines published on the IOF website [1,3,107,111,120,127,141], there seem to be no established screening programmes for osteoporosis in the general population in the EU. The following section therefore presents an overview of the approaches for identifying patients at risk of osteoporotic fractures reported

in US, Canadian and European guidelines for screening. However, this compilation is not necessarily comprehensive. Furthermore, the systematic representation of clinical guideline recommendations from Europe usually presented in the appendix was not expected to be helpful in this context and was therefore omitted.

See also question [B0001] for this question and [A0002] for the criteria for the operational definition of osteoporosis. With slight variations, this definition seems to be widely accepted, but is not the basis on which treatment decisions are being made. The algorithms on which treatment decisions are based vary in the different countries. Even if countries use the FRAX tool, algorithms and treatment thresholds will vary due to the country-specific adaptations made in the tool [1].

In women of 65 years or older, both the USPTF and the Canadian guideline recommend screening for osteoporosis using BMD measurement [8,142]. For women younger than 65 years, screening using BMD measurement is recommended if they are at an increased risk of osteoporosis based on an assessment with a standard clinical risk assessment tool [8]. According to the USPTF, several tools (osteoporosis self-assessment tool [OST], osteoporosis risk assessment instrument [ORAI], osteoporosis index of risk [OSIRIS], simple calculated osteoporosis risk estimation [SCORE], and FRAX) can be used for this risk assessment, as their performance is similar, although the number of risk factors recorded varies [8]. Women younger than 65 years will be eligible for BMD measurement if the estimated risk of MOF is the same or greater than that of a 65 year old woman without major risk factors [8]. For men, the guideline deemed the evidence to be insufficient to assess the balance of benefits and harms [8].

In Canada, women aged 50 to 64 years with at least one of the following risk factors are eligible for BMD measurement: fragility fracture after the age of 40 years, prolonged glucocorticoid use, parental hip fracture, aromatase inhibitor use, vertebral fracture, high alcohol intake, current smoking, low body weight (< 60 kg), major weight loss (> 10 % of weight at age 25), and other disorders strongly associated with osteoporosis [142]. Both strategies were investigated with regard to their predictive power. As sensitivities and specificities were often low, it was suggested to adapt screening and treatment algorithms [142].

The DVO guideline for Germany, Austria, and Switzerland defines other BMD cut-offs for the initiation of treatment depending on the presence or absence of other clinical risk factors, such as the presence of previous fragility fractures or the planned treatment with glucocorticoids [104]. The DVO has developed its own risk score and strongly advocates its use in preference to other tools in German-language countries, as it is based on current German, Austrian, and Swiss data and in their opinion considers all the relevant risk factors [10]. The model does not adjust for the competing risk “mortality”, as it was felt that this leads to lower thresholds for older patients and would affect equity across age groups [10].It has been validated as part of the FREEDOM trial [10]. Risk factors were classified as moderate, strong, and very strong, and prevalent fractures are taken into consideration grouped by degrees in order to obtain a more individual fracture risk estimate [10]. A re-evaluation of the risk assessment tool was planned for 2018 pending the publication of a study from Sweden and 2 studies from Canada [10].The guideline authors point out that there are many rare diseases that may warrant diagnostic work-up of patients and are not covered by the risk score; these issues are addressed in separate sections of the guideline [10]. For women and men aged 70 years or older, a diagnostic work-up is recommended if this can be justified by the treatment planned [10]. Separate recommendations for Switzerland by the Swiss Association against Osteoporosis (Schweizerische Vereinigung gegen die Osteoporose, SVGO) describe the relative risks of fractures in the presence of individual risk factors and specify in which instances DXA is covered by statutory health insurance; they also state that the fracture risk can be assessed with FRAX [143].

The NICE guideline from 2017 recommends that a fracture risk assessment should be considered in all women aged 65 years and over and all men aged 75 years and over [107]. In addition, it should be considered in women aged under 65 years and men aged under 75 years with risk factors, such as previous fragility fracture, history of falls, or current use or frequent recent use of oral or systemic glucocorticoids [107]. The guideline recommends to "not routinely assess fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk" [107]. The QFracture tool is suggested as an alternative risk factor tool for the FRAX tool in the NICE guideline [107], while the SIGN guideline of 2015 recommends that the QFracture tool should be the preferred tool for the risk assessment for fractures, "prior to DXA in patients with clinical risk factors for osteoporosis and in whom osteoporosis treatment is being considered" [144].

Advocates for the use of FRAX estimated that the number eligible for treatment with QFracture would be 12,300 women versus 81,700 women with FRAX [144]. They argued that this difference is due to poor calibration of the QFracture tool rather than an overestimate of the fracture risk by the FRAX tool. According to these authors, treatment thresholds based on T-scores of -2.5 or worse are problematical because they are based on false assumptions: "First […] most fragility fractures occur in individuals with a BMD T-Score above the operational threshold for osteoporosis […]. Second any given T-score threshold has a different significance at different ages […]." As "with advancing age the difference in the probability of fracture between the general population and those with a T-score of -2.5 SD diminishes […]" [144]. Other false assumptions mentioned are that high FRAX scores do not identify patients with low BMD and that treatment for osteoporosis is only beneficial in osteoporosis that has been confirmed based on a low BMD [144].

The Italian guideline from 2016 recommends BMD in women who are at least 65 years old and men who are at least 70 years old, in patients of any age with previous fragility fractures, osteoporosis based on x-ray, or major risk factors for osteoporosis [111]. They also recommend testing in people who are 60 years or older if certain risk factors are present, such as early menopause or prolonged immobility [111].

According to the Polish guideline of 2017, for the Polish population, primary care doctors can identify patients at risk of fractures based on physical examination, history of fractures and falls, and risk assessment via FRAX BMI and refer people to a specialist centre or osteoporosis clinic for further assessment [127]. According to the survey of EUnetHTA partners, a formal screening programme is due to start in Poland in 2023.

[A0025] – How is osteoporosis currently managed according to published guidelines and in practice?

Besides general preventive measures [10], specific drug treatments are available. Several drugs have been shown to be effective for the treatment of osteoporosis and guidelines suggest that the choice of drug needs to be adapted to the individual patient, rather than recommending a clear treatment strategy with first-line and second-line treatments [1,3,8,10,111]. The guidelines often present overviews of the drug effects similar to Table 3-1, often with detailed descriptions of the available evidence on benefits and harms [1,3,8,10,111] (see also answer to question [B0001]).

4.2.4 Target population

[A0007] – What is the target population in this assessment? and

Part I [A0023] How many people belong to the target population in the different European countries? (For part II see [A0002]: Are there differences in the epidemiology?)

The initial target population is the general population. No age cut-offs have been pre-defined. For information on how many people are suffering from osteoporosis in the different European countries and differences in the epidemiology, see answers to question [A0002].

The ROSE trial in Denmark gives some indication of the potential number of people that might be eligible for screening. Of the 17,072 people randomised to the screening arm who were sent a FRAX questionnaire, 13,409 (79 %) responded. For 10,411 people (61 %), the fracture risk could be calculated based on their answers; of these 10,411 people, 1132 (11 %) were already on treatment for osteoporosis. Of the remaining 9,279 people, 7,056 (76 %) had a FRAX score ≥ 15 % and were offered a DXA scan. The DXA scan was offered to 6,226 people (88 % of the eligible population) who were interested in testing; of these, 5,009 (80 %) were actually scanned. Treatment for osteoporosis was indicated in 1,236 (25 %) of people who had been scanned and 986 (80 %) received treatment [17].

[A0011] – How much is screening for osteoporosis practised in Europe to guide pharmacological management and fracture prophylaxis?

Based on the results of the survey of EU members, screening in the general population has not yet been established in Europe (see also answer to question [B0003]). In Poland, a screening programme in the general population is currently being set up and is due to be operational from 2023 onwards.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of screening for osteoporosis on mortality?
D0005	How does screening affect symptoms and findings (severity, frequency) of osteoporosis?
D0006	How does the screening for osteoporosis in the general population affect progression of the disease or health condition?
D0011	How does screening for osteoporosis affect body function?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of screening for osteoporosis on generic health-related quality of life?
D0013	What is the effect of screening for osteoporosis on generic disease-specific quality of life?

5.2 Results

5.2.1 Studies included

Core study pool: RCTs with marker-based strategy design

In the information retrieval, 3 “conventional” RCTs assessing an entire screening-treatment process were identified as relevant for this Rapid REA: the SCOOP study [16], the ROSE study [17], and the COSHIBA study [18].

A total of 49,912 postmenopausal women were examined in these strategy design RCTs: 24,367 women were allocated randomly to the intervention arm and 25,545 women to the control arm. The women were between 65 and 85 years old. The 2 largest RCTs were the ROSE trial [17], conducted in Denmark, and the SCOOP trial [16], conducted in the UK. The women from the ROSE Trial were randomly selected via the Danish Civil Registration System and randomised before recruitment, stratified by age and region. Data from the public register could be linked with data from health registers so that information on fractures, co-morbidities, and prescriptions of anti-osteoporosis drugs could be obtained from the registers and data could also be obtained from drop-outs. In SCOOP, on the other hand, the women were identified on the basis of primary care lists. Information on outcomes was obtained from several sources: participants self-reporting fractures, routine hospital episode statistics data, and primary care records were used as well as data from the Office of National Statistics for information on deaths. Both studies employed a similar 3-tiered screening approach consisting of a fracture risk assessment (FRAX score), bone density measurement (DXA), and anti-osteoporosis drug treatment according to local standards. In SCOOP, the participation rate was 32.9 % while in ROSE about 61 % of randomised participants could be included with the FRAX calculated.

The follow-up in both studies was 5 years. Several fracture categories were investigated. In addition, SCOOP reported results on mortality and HrQoL.

The third strategy-design RCT was the smaller COSHIBA trial [18]. This trial was conducted by the University of Bristol, UK, and recruited participants from multiple general practices within the Bristol area. The chosen screening approach differed from the approaches of SCOOP and ROSE: 3,200 postmenopausal women between 65 and 80 years of age were randomised in a 1:2 ratio to a

screening and a control group after completing a questionnaire that collected baseline data. The participation rate was 45.2 % and thus lies between the SCOOP and ROSE rates. In the screening group, height loss, history of previous non-vertebral fractures, the Margolis back pain score, and the rib-to-pelvis distance were assessed as risk factors. Women identified as being at a high risk of fracture were offered a thoracolumbar radiograph. Treatment was left up to the attending GP. The outcomes were self-reported new fractures at 6 and 12 months of follow-up. To collect these outcomes, questionnaires were posted to all the participants, but the specifications given were not verified. Follow-up was 1 year.

Supportive study pool: RCTs with enrichment design

In addition, 5 enrichment design RCTs were included as additional evidence. In 2 RCTs, performed in the USA in the 1990s, a total of 6,459 women between 55 and 81 years of age were treated with either alendronate (n = 3,236) or placebo (n = 3,223). These were the 2 sub-studies of the Fracture Intervention Trial (FIT), which differed in that 1 sub-study (i.e. the Clinical Fracture study [19]) included only women without pre-existing vertebral fractures, but with a T-score of ≤ -2.5 SD, while the other sub-study (i.e. Vertebral Deformity study [20]) included only women with decreased BMD and with ≥ 1 pre-existing vertebral fracture. In the joint recruitment procedure, women from the general population were contacted by means of mass mailings and screened with DXA. Women were included in the study if the T-score was ≤ -1.6 SD. The trial provided data on fractures, back pain, utilisation of healthcare resources, mortality, and adverse events. Follow-up was 4.2 years (mean) in the Clinical Fracture study and 3 years (mean) in the Vertebral Deformity study. Due to the independent sample size calculation and randomisation, the FIT sub-studies are counted as 2 RCTs in this Rapid REA.

In addition, a recent RCT from New Zealand, Reid 2018 [23], was included. 2,000 postmenopausal women from the Auckland region were recruited using electoral registers. They were included if they were ≥ 65 years old and had a T-Score of -1.0 to -2.5 SD at either the total hip or the femoral neck on either side. They were randomly assigned to receive 4 infusions of either zoledronic acid at a dose of 5 mg or normal saline at 18 months intervals. Follow-up was 6 years. The trial provided data on fractures, adverse events, and mortality.

In 2 further RCTs from China, postmenopausal women were randomly assigned to be treated with either once yearly intravenous zoledronic acid or matching placebo after being recruited from the general population. In Liang 2017 [21], 285 women were screened with DXA and a blood test (for routine chemical and bone turnover markers analysis) prior to randomisation. Women were followed for 2 years. In Yang 2015 [22] only a DXA testing was performed before randomisation of women (n = 100). Follow-up was 1 year. In the 2 FIT sub-studies, clinical fractures, back pain, mortality, and adverse events were assessed, while the trials from China provided evaluable data on adverse events [21,22], fractures, and mortality [22].

Studies formally included

RCTs with marker-based strategy design

Yuksel 2009 [24] is a small RCT with a total of 262 participants included. Community pharmacists in the province of Alberta, Canada, recruited individuals ≥ 65 or between 50 and 64 years with at least 1 risk factor for osteoporotic fractures. Both persons already treated for osteoporosis and persons with BMD measurements within the last 2 years were excluded. Subsequently, participants were randomly allocated to either the screening arm or the control arm. The intervention consisted of a separate 30-minute appointment with an information session and a qUS measurement at the heel. The persons were then sent to their GP, who arranged for an examination with DXA, if deemed necessary. Patient-relevant outcomes (i.e. generic health status [SF-12] and osteoporosis-specific quality of life [OPTOQoL]) were recorded in the pharmacy after 16 weeks. The duration of this study

was very short. It was only formally included but its results were not considered, since at the end of the follow-up only 63 % (intervention arm) and 69 % (control arm) of all study participants had data available.

RCTs with enrichment design

Chesnut 1995 [25] formally met the required inclusion criteria. Postmenopausal women were recruited by advertisements and medical announcements and were included if BMD was ≤ 2 SD. Exclusion criteria were any disease or drug therapy potentially affecting bone metabolism or presence of spine or hip fractures attributable to osteoporosis. After recruitment, participants were randomly assigned to either placebo or 5 different regimens of alendronate. The follow-up was 2 years. The primary aim of the study was to investigate alendronate`s effect on biochemical markers of bone remodelling and calcium metabolism. However, as the authors did not provide results on patient-relevant outcomes separately for each study arm (adverse events, fractures), this study could only be formally included in the Rapid REA. The study is not presented in detail and its data not considered.

Assessment of the risk of bias at the study and outcome level

Study level

The risk of bias at the study level was rated as low for 2 of the 3 strategy design studies: ROSE [17] and SCOOP [16]. For COSHIBA [18], the risk of bias was rated as high, since it remained unclear whether allocation concealment had been adequate.

The risk of bias at the study level was rated as low for Reid 2018 [23]. However, in the 2 FIT trials (Liang 2017 and Yang 2015), it remained unclear whether an allocation concealment had been adequate [19-22]. In addition, for Yang 2015 [22], it was unclear whether doctors had been blinded. Furthermore, for both Liang 2017 and Yang 2015, information was lacking on whether the randomisation sequence generation had been adequate [21,22]. Therefore, the risk of bias at the study level was assessed as high for all trials with enrichment design, with the exception of Reid 2018. An overview is given in Table A-9 (see Appendix 1).

Outcome level

The risk of bias for symptomatic fractures was rated as low, since the risk of bias in the 2 large strategy design RCTs SCOOP [16] and ROSE [17] was rated as low. In the enrichment design study pool reporting on this outcome, the overall risk of bias was rated as high, because the risk of bias on the study level was rated as high in 4 out of 5 trials. In addition, in Liang 2017 and Yang 2015, selective outcome reporting was likely, since no study registry entry could be identified [21,22]. Apart from that, it was unclear whether in Yang 2015 [22] the outcome assessors were blinded.

For mortality, the risk of bias was rated as low, since SCOOP provided evidence on this outcome with a low risk of bias. In the enrichment design study pool the risk of bias was rated as high, because the risk of bias on the study level was rated as high in 3 out of 4 trials reporting on this outcome.

For the outcome “utilisation of healthcare resources”, only data from 1 enrichment design study were available. Since the risk of bias on the study level was rated as high and the blinding of the outcome assessors was deemed unclear, the risk of bias on the outcome level was also rated as high.

For HrQoL, SCOOP provided data with a high risk of bias since the outcome assessors were not blinded [145].

Data on (serious) adverse events were only available from studies with an enrichment design. The 2 FIT trials [19,20] provided data on this outcome if alendronate formed part of the screening-treatment strategy. Since the risk of bias on the study level was high, the risk on the outcome level was also rated as high. Liang 2017 [21] and Yang 2015 [22] both provided data on adverse and serious adverse events if zoledronic acid was part of the approach. For these studies, the risk of bias on the study level was rated as high. In addition, in Liang 2017 [21] the ITT principle was not adequately implemented and in Yang 2015 [22] it remained unclear whether the outcome assessors had been blinded. Therefore, the risk of bias on the outcome level was rated as high. Reid 2018 [23], investigating zoledronic acid as part of the approach, provided data on serious adverse events with a low risk of bias.

An overview is given in Tables A-10 to A-15 in Appendix 1.

Quality of the evidence

The assessment of the outcome-specific quality of the evidence is presented in Tables A-16 to A-27 in Appendix 1.

5.2.2 Mortality

[D0001] – What is the expected beneficial effect of screening for osteoporosis in the general population on mortality?

Results from RCTs with marker-based strategy design

Data on mortality were assessed in 1 strategy design RCT [16]. There was no statistically significant difference between the 2 arms adjusted for recruiting region, baseline FRAX probability, and falls.

Table 5-1: Proportion of women who died – Marker-based strategy design

Study / Outcome	Screening			No Screening			Screening vs. No Screening		
	N	Women who died		N	Women who died		HR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
SCOOP [16]									
Mortality	6,233	550	8.8	6,250	525	8.4	1.05[a]	[0.93; 1.19][a]	0.436[a]

a: HR, CI and p value: Cox PH model adjusted for recruiting region, baseline FRAX probability, and falls

Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated

Conclusion on the quality of the evidence and on mortality

Screening for osteoporosis results in little or no difference in mortality compared with no screening. This conclusion is based on high quality evidence.

Supplementary presentation: Results from RCTs with enrichment design

Additional data were available from the 2 FIT sub-trials [19,20], from Reid 2018 [23], and from Yang 2015 [22].

Due to content issues (i.e., mainly different forms of drug administration), the FIT trials were assessed separately. Since different effect measures were reported for the 2 FIT sub-studies, the data were not pooled. In Yang 2015 no deaths occurred in either study arm. None of the studies examining this outcome found statistically significant effects.

Table 5-2: Proportion of women who died – Enrichment design

Study / Out-come	Treatment			Placebo			Treatment vs. Placebo		
	N	Women who died		N	Women who died		HR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT Clinical Fracture study [19]									
Mortality	2,214	37	1.7	2,218	40	1.8	0.92[a]	[0.59; 1.45][a]	ND
FIT Vertebral Deformity study [20]									
Mortality	1,022	21	2.1	1,005	24	2.3	1.13[b,c]	[0.62; 2.04][b]	0.687[d]
Reid 2018 [23]									
Mortality	1,000	27	2.7[e]	1,000	41	2.3[e]	0.65	[0.40; 1.05]	ND
Yang 2015 [22]									
Mortality	50	0	0	50	0	0	ND	ND	ND

a: from likelihood ratio method
b: Rapid REA authors` own calculation
c: OR
d: Mantel-Haenszel Chi square
e: Rapid REA authors' own calculation
Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; odds ratio; REA: relative effectiveness assessment

The quality of the evidence was rated as very low in the enrichment design RCTs. The overall risk of bias at the outcome level was rated as high. In addition, the quality of the evidence was down-graded by 2 levels due to indirectness.

5.2.3 Morbidity

[D0005] – How does screening affect symptoms and findings (severity, frequency) of osteoporosis?

5.2.3.1 Symptomatic fractures

In some studies, the terms "osteoporotic fractures" and "fragility fractures" are used synonymously. Therefore, in this Rapid REA, the term "osteoporotic fractures" includes "fragility fractures", as long as it summarises clinical (symptomatic) fractures.

The results of all sub-outcomes of symptomatic fractures reported in the studies included (for an overview see Table 0-1 and Table 1-2) are presented below. A summarised conclusion on benefit for the overall outcome "symptomatic fractures" is given at the end of this section.

Clinical fractures

In the strategy design studies, clinical fractures were operationalised as "any clinical fractures".

Results from RCTs with marker-based strategy design

Results from 2 strategy design RCTs were available [16,18]. In addition to content issues (mainly different screening approaches), the fact that different effect measures were used prevented a meta-analysis of the results. In the SCOOP and COSHIBA trials, no statistically significant difference could be observed between the 2 study arms.

Table 5-3: Proportion of women with clinical fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with clinical fractures		N	Women with clinical fractures		HR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
SCOOP [16]									
Any clinical fractures[a]:	6,233	951	15.3	6,250	1,002	16.0	0.94[b]	[0.86; 1.03][b]	0.183[b]
COSHIBA [18]									
Self-reported new fractures[c]	1,062	21	2.0	2,138	75	3.5	0.6[d]	[0.35; 1.03][d]	0.063

a: included all occurring fractures, including fractures of the hands, feet, ankle, face, and skull
b: HR, CI, and p value: Cox PH model adjusted for recruiting region, baseline FRAX probability, and falls
c: forearm, hip, vertebral, other
d: OR, using logistic regression

Abbreviations: CI: confidence interval; FRAX: Fracture Risk Assessment Tool; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; OR: odds ratio, SHR: sub-hazard ratio

Conclusion on the quality of the evidence

The overall quality of the evidence for this outcome was high, since SCOOP and COSHIBA provided high-quality evidence.

Supplementary presentation: Results from RCTs with enrichment design

Results from the 2 sub-studies of the FIT trial [19,20] and from Reid 2018 [23] on clinical fractures were available. In addition, in both Yang 2015 [22] and in Liang 2017 [21] it was reported that no fractures occurred during the follow-up.

The operationalisation in the 2 FIT trials excluded facial and skull fractures, pathological fractures, and those fractures due to trauma but sufficient to fracture a normal bone in most young adults. Symptomatic vertebral fractures and all non-vertebral fractures from Reid 2018 are grouped under the term “clinical fractures” in this Rapid REA. In the 2 Chinese studies, the operationalisation remained unclear. Nevertheless, the results were considered together because the agreement between the operationalisations used was assessed as sufficient.

The results of the 2 FIT sub-studies are homogeneous, so that a pooled effect estimator from a meta-analysis, which was calculated using a fixed effect model (inverse variance), was available. The pooled effect was statistically significant (p = 0.001). A statistically significant difference in favour of the intervention was also observed in Reid 2018 (p = 0.003).

The results table and the forest plot on enrichment design studies are presented below.

Table 5-4: Proportion of women with clinical fractures – Enrichment design

Study / Outcome operationalisation	Treatment N	Treatment Women with clinical fractures n	Treatment Women with clinical fractures %	Placebo N	Placebo Women with clinical fractures n	Placebo Women with clinical fractures %	Treatment vs. Placebo HR	Treatment vs. Placebo [95 % CI]	Treatment vs. Placebo p value
Enrichment design									
FIT Clinical Fracture study [19]									
Any clinical fracture[a]	2,214	272	12.3	2,218	312	14.1	0.86[b]	[0.73; 1.01][b]	0.07[c]
FIT Vertebral Deformity study [20]									
Any clinical fracture[d]	1,022	139	13.6	1,005	183	18.2	0.72	[0.58; 0.90]	ND
Liang 2017 [21]									
Fractures[e]	155	0	0	95	0	0	ND	ND	ND
Reid 2018 [23]									
Symptomatic fractures[f]	1,000	163	16.3[g]	1,000	214	21.4[g]	0.73	[0.60; 0.90]	0.003
Yang 2015 [22]									
Fractures[h]	50	0	0	50	0	0	ND	ND	ND

a: pathologic fractures or fractures due to trauma sufficient to fracture a normal bone in most young adults excluded; facial and skull fractures excluded

b: HR, CI: likelihood ratio method

c: calculated with log-rank test

d: including non-spine and clinical vertebral fractures

e: operationalisation in the publication is “fragility fracture”

f: operationalisation in the publication is “symptomatic fracture”; it includes symptomatic vertebral fractures and any nonvertebral fractures

g: Rapid REA authors’ own calculation

h: no operationalisation available

Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; REA: relative effectiveness assessment

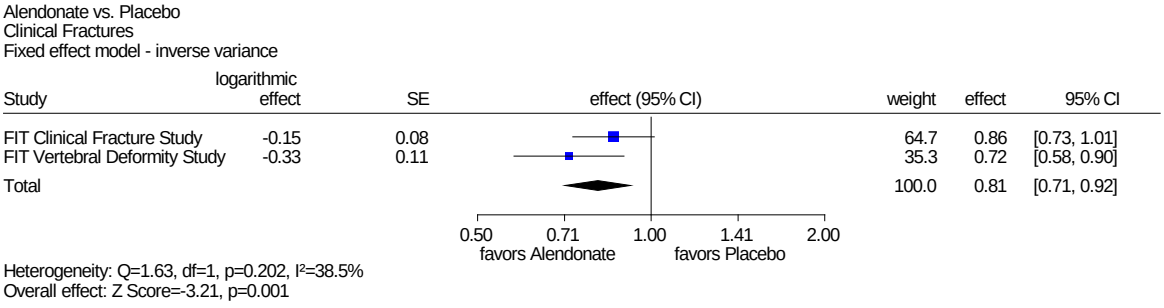

Figure 2: Forest plot on clinical fractures, effect measure: hazard ratio – additional evidence

The evidence from the enrichment design RCTs offered only evidence of very low quality, since downgrading was required due to the overall high risk of bias and indirectness (due to enrichment design).

Major osteoporotic fractures

Major osteoporotic fractures were operationalised as hip, clinical vertebral, wrist, or humerus fractures.

Results from RCTs with marker-based strategy design

Only data from 1 strategy design study (ROSE [17]) were available for this outcome.

The sub-hazard ratio (derived from Fine-Gray competing risk of death regression model for time from index date to fracture) was 0.99 (95 % CI [0.92; 1.06]). No statistically significant effect was observed (p = 0.736).

The results table is presented below.

Table 5-5: Proportion of women with major osteoporotic fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with MOF		N	Women with MOF		HR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
ROSE [17]									
Major osteoporotic fractures[a]	17,072	1,697	9.9	17,157	1,719	10.0	0.99[b]	[0.92; 1.06][b]	0.736

a: hip, clinical vertebral, wrist or humerus fracture

b: SHR from competing risk of death regression model

Abbreviations: CI: confidence interval; HR: hazard ratio; MOF; major osteoporotic fractures; n: number of patients with event; N: number of patients evaluated; SHR: sub-hazard ratio

Conclusion on the quality of the evidence

The quality of the evidence was rated as high for the sub-outcome major osteoporotic fractures.

Osteoporosis-related fractures

Osteoporosis-related fractures were operationalised as all fractures excluding the hands, feet, nose, skull, or cervical vertebrae in the SCOOP trial and as all potential osteoporotic fractures, excluding fractures of the fingers, toes, skull, or face in the ROSE trial.

Results from RCTs with marker-based strategy design

Data from 2 strategy design studies were available for this outcome.

Since the results were homogeneous, they could be summarised in a meta-analysis (fixed effect model, inverse variance). No statistically significant effect was observed, neither in the 2 individual studies nor after their quantitative summary.

The results table and the forest plot on studies with enrichment design are presented below.

Table 5-6: Proportion of women with osteoporosis-related fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with ORF		N	Women with ORF		HR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
SCOOP [16]									
Osteoporosis-related fractures[a]	6,233	805	12.9	6,250	852	13.6	0.94[b]	[0.85; 1.03][b]	0.178
ROSE [17]									
All potential osteoporotic fractures[c]	17,072	2,238	13.1	17,157	2,233	13.0	1.01[d]	[0.95; 1.07][d]	0.871

a: all fractures excluding the hands, feet, nose, skull, or cervical vertebrae; vertebral fractures documented within 6 months of randomisation were excluded due to uncertainty about the actual date of occurrence

b: adjusted for recruiting region, baseline FRAX probability, and falls

c: excluding fractures of fingers, toes, skull, or face

d: SHR from competing risk regression model

Abbreviations: CI: confidence interval; FRAX: Fracture Risk Assessment Tool; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ORF: osteoporosis-related fractures; SHR: subhazard ratio

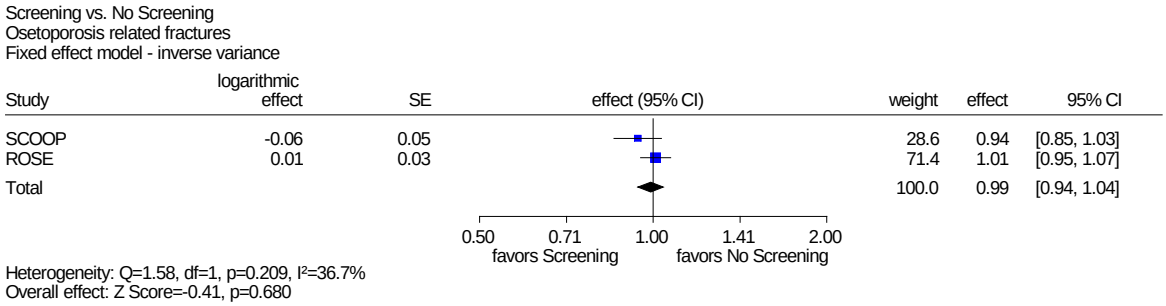

Figure 3: Forest plot on osteoporosis-related fractures, effect measure: hazard ratio

Conclusion on the quality of the evidence

The overall quality of the evidence was rated as high for this outcome, since SCOOP and ROSE both provided high-quality evidence.

Clinical vertebral fractures

Results from RCTs with marker-based strategy design

For this outcome, data were available from 1 strategy design RCT [18]. No statistically significant effect was observed. The results table is presented below.

Table 5-7: Proportion of women with clinical vertebral fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with CVF		N	Women with CVF		OR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
COSHIBA [18]									
Clinical vertebral fractures	1,062	1	0.1	2,138	6	0.3	0.33[a]	[0.04; 2.79][a]	0.324[a,b]

a: Rapid REA authors` own calculation

b: unconditional exact method (CSZ-method [146])

Abbreviations: CI: confidence interval; CVF: clinical vertebral fractures; n: number of patients with event; N: number of patients evaluated; OR: odds ratio; REA: relative effectiveness assessment

Conclusion on the quality of the evidence

The quality of the evidence in COSHIBA was rated as low. Limiting factors were a high risk of bias and serious imprecision because of a large CI.

Supplementary presentation: Results from RCTs with enrichment design

Results on clinical vertebral fractures were also available from the 2 sub-studies of the FIT trial [19,20] and from Reid 2018 [23].

A stratified proportional hazards model was used to estimate the RR and calculate the 95 % CI from data from the 2 FIT trials [70]. The pooled estimate was statistically significant (p = 0.001). The difference between the intervention and control arm in Reid 2018 was also statistically significant (p = 0.004).

Table 5-8: Proportion of women with clinical vertebral fractures – Enrichment design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with CVF		N	Women with CVF		RR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT (Clinical Fracture study and Vertebral Deformity study [70]**)**									
First symptomatic vertebral fracture	3,236	ND	ND	3,223	ND	ND	0.53[a]	[0.36; 0.77][a]	0.001[b]
Reid 2018 [23]									
Symptomatic vertebral fracture	1,000	14	1.4[c]	1,000	34	3.4[c]	0.41[d]	[0.22; 0.75]	0.004

a: RR and CI: stratified proportional hazard model

b: stratified log-rank test

c: Rapid REA authors` own calculation

d: HR

Abbreviations: CI: confidence interval; CVF: clinical vertebral fracture; n: number of patients with event; HR: hazard ratio; N: number of patients evaluated; ND: no data; REA: relative effectiveness assessment; RR: relative risk

In the enrichment design trials, the quality of evidence was rated as very low. There was an overall high risk of bias and very serious indirectness due to the enrichment design. Therefore, the quality of the evidence was downgraded by 3 levels.

Other clinical fractures

Other clinical fractures were operationalised as fractures other than those of the hip, forearm / wrist, or spine.

Results from RCTs with marker-based strategy design

Data were available from 1 strategy design study [18]. In this study no statistically significant effect was observed for this outcome (p = 0.219).

Table 5-9: Proportion of women with other clinical fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with OCF		N	Women with OCF		OR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
COSHIBA [18]									
fractures other than hip, forearm, vertebral fractures	1,062	11	1.0	2,138	34	1.6	0.65[a]	[0.33; 1.28][a]	0.219[a,b]

a: Rapid REA authors` own calculation

b: unconditional exact method (CSZ-method [146])

Abbreviations: CI: confidence interval; OCF: other clinical fractures; OR: odds ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; REA: relative effectiveness assessment

Conclusion on the quality of the evidence

The quality of the evidence was rated as low for this outcome. In COSHIBA, the quality of the evidence was downgraded by 2 levels due to the high risk of bias and serious imprecision caused by the fact that results could only be derived from 1 small study with this screening approach.

Supplementary presentation: Results from RCTs with enrichment design

Data were also available from the 2 sub-studies of the FIT trial [19,20].

Since data from the 2 FIT sub-trials were homogeneous, they could be combined in a meta-analysis (fixed effect model, inverse variance). The pooled estimate was statistically significant (p = 0.047).

The results table and the forest plot on studies with enrichment design are presented below.

Table 5-10: Proportion of women with other clinical fractures – Enrichment design

Study / Outcome operationalisation	Treatment			Placebo			Screening vs. Placebo		
	N	Women with OCF		N	Women with OCF		HR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT Clinical Fracture study [19]									
Other fractures[a]	2,214	182	8.2	2,218	227	10.2	0.79	[0.65; 0.96][b]	0.02[c]
FIT Vertebral Deformity study [20]									
Other fractures[d]	1,022	100	9.8	1,005	99	9.9	0.99	[0.75; 1.31][e]	ND

a: fractures other than hip, wrist or spine

b: likelihood ratio method

c: log-rank test

d: shoulder, arm, hand, fingers, ribs, chest, pelvis, coccyx, sacrum, leg, ankle, foot, toes, peri-prosthetic

e: proportional hazard model with likelihood ratio method

Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; OCF: other clinical fractures

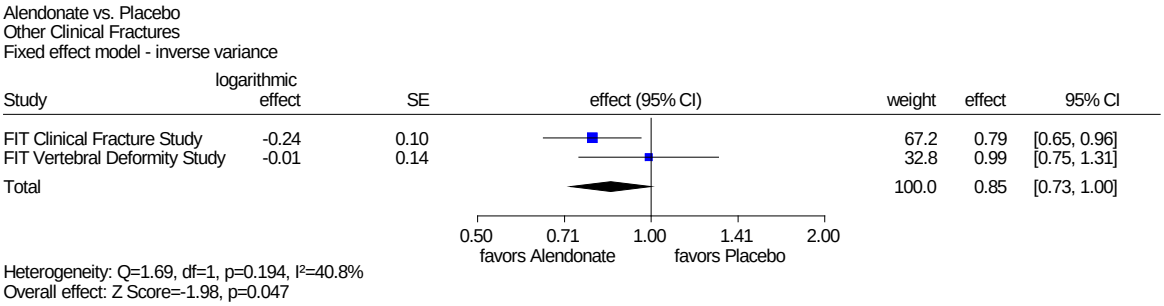

Figure 4: Forest plot on other clinical fractures, effect measure: hazard ratio – additional evidence

In the FIT study, there was a high risk of bias and very serious indirectness due to the enrichment design. The quality of evidence was downgraded accordingly.

Hip fractures

Results from RCTs with marker-based strategy design

Hip fractures were assessed in all 3 strategy design studies.

In a meta-analysis an attempt was made to combine results from the SCOOP and ROSE trials quantitatively. Due to content issues (i.e. different screening approaches, shorter follow-up periods, different effect measures), COSHIBA was not added to the quantitative summary. However, significant heterogeneity was found. One possible reason for this could be a difference in the designs of SCOOP and ROSE. This issue is addressed in the discussion section.

The qualitative summary is shown in the figure below.

Table 5-11: Proportion of women with hip fractures – Marker-based strategy design

Study / Outcome operationalisation	Screening			No Screening			Screening vs. No Screening		
	N	Women with Hip Fractures		N	Women with Hip Fractures		HR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
SCOOP [16]									
Hip fractures[a]	6,233	164	2.6	6,250	218	3.5	0.72[b]	[0.59; 0.89][b]	0.002
ROSE [17]									
Hip fractures	17,072	534	3.1	17,157	532	3.1	1.01[c]	[0.89; 1.14][c]	0.903
COSHIBA [18]									
Hip fractures	1,062	3	0.28	2,138	6	0.3	1.01[d,e]	[0.25; 4.71][d]	> 0.999 [d,f]

a: verified fractures with a specific description of neck of femur or proximal femur. Fractures described as subtrochanteric, femoral shaft, distal femur, or simply femoral were not categorised as hip fractures

b: HR, CI, and p value: Cox proportional hazards model, adjusted for recruiting region, baseline FRAX probability, and falls

c: SHR from competing risk regression model

d: Rapid REA authors` own calculation

e: OR

f: unconditional exact method (CSZ-method [146])

Abbreviations: CI: confidence interval; FRAX: Fracture Risk Assessment Tool; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; OR: odds ratio; REA: relative effectiveness assessment; SHR: sub-hazard ratio

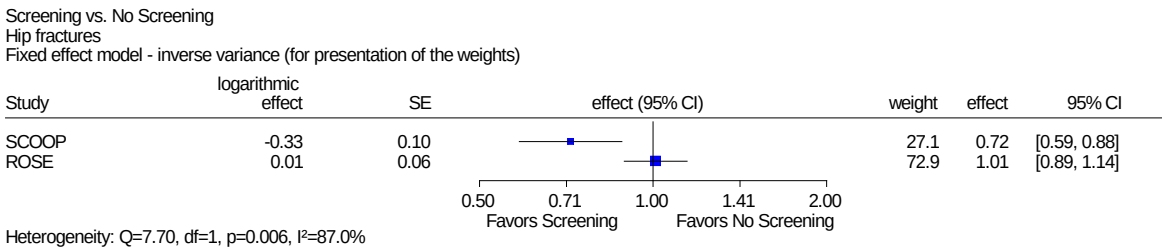

Figure 5: Forest plot on hip fractures, effect measure: hazard ratio

Conclusion on the quality of the evidence

The quality of the evidence for the core study pool was downgraded by 1 level because of inconsistent results and differences in study design.

Supplementary presentation: Results from RCTs with enrichment design

Data on hip fractures were assessed in both sub-studies of the FIT trial [19,20] and in Reid 2018 [23].

In the 2 sub-studies of the FIT trial, no statistically significant effect was observed, neither in the individual studies nor in a meta-analysis (fixed effect model, inverse variance). Due to content issues (i.e. different drugs, different follow-up periods), data from the FIT trials were not pooled with data from Reid 2018. However, the effects observed in Reid 2018 were not statistically significant.

The results tables and the forest plot on studies with enrichment design are presented below.

Table 5-12: Proportion of women with hip fractures – Enrichment design

Study	Treatment			Placebo			Treatment vs. Placebo		
Outcome operationalisation	N	Women with hip fractures		N	Women with hip fractures		HR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT Clinical Fracture study [19]									
Hip fractures	2,214	19	0.9	2,218	24	1.1	0.79[a]	[0.43; 1.44][a]	0.44[b]
FIT Vertebral Deformity study [20]									
Hip fractures	1,022	11	1.1	1,005	22	2.2	0.9[c]	[0.23; 0.99][c]	ND
Reid 2018 [23]									
Hip fractures	1,000	8	0.8[d]	1,000	12	1.2[d]	0.66	[0.27; 1.16]	Not statistically significant

a: likelihood ratio method
b: log-rank test
c: proportional hazard model with likelihood ratio method
d: Rapid REA authors` own calculation
Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; REA: relative effectiveness assessment

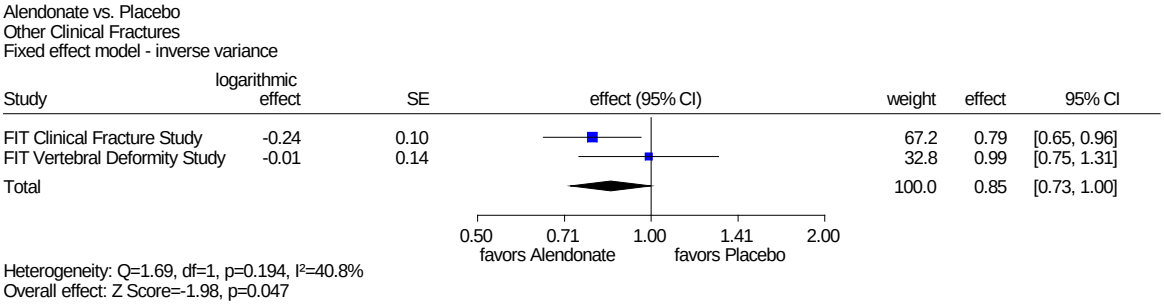

Figure 6: Forest plot on hip fractures, effect measure: hazard ratio – additional evidence

In the studies with an enrichment design, the overall risk of bias was rated as high and due to serious inconsistency (enrichment design), the quality of evidence was downgraded accordingly. The quality of the evidence in the additional study pool was therefore very low.

Wrist fractures

Results on RCTs with marker-based strategy design

Data on wrist and forearm fractures were available from 1 strategy design RCT [18]. A statistically significant effect in favour of the intervention was observed (p = 0.043).

Table 5-13: Proportion of women with forearm fractures – Marker-based strategy design

Study / Outcome definition	Screening			No Screening			Screening vs. No Screening		
	N	Women with forearm fractures		N	Women with forearm fractures		OR	[95 % CI]	p value
		n	%		n	%			
Marker-based strategy design									
COSHIBA									
Forearm fractures	1,062	6	0.57	2,138	29	1.36	0.41[a]	[0.17: 1.00][a]	0.043[a,b]

a: Rapid REA authors` own calculation

b: unconditional exact method (CSZ-method [146])

Abbreviations: CI: confidence interval; n: number of patients with event; N: number of patients evaluated; OR: odds ratio; REA: relative effectiveness assessment

Conclusion on the quality of the evidence

The quality of the evidence in COSHIBA was downgraded by 2 levels due to a high risk of bias and serious imprecision due to the fact that the results were derived from only 1 small study with this screening approach (lack of replication).

Supplementary presentation: Results from RCTs with enrichment design

Results were also available from the 2 FIT sub-studies with enrichment design [19,20] and from Reid 2018 [23].

Due to statistically significant heterogeneity, the data of the 2 FIT sub-studies on wrist fractures could not be summarised quantitatively in a meta-analysis. While the sub-study including women with vertebral fractures (Vertebral Deformity study) showed a statistically significant effect in favour of the intervention, this was not the case in the sub-study including women without pre-existing vertebral fractures (Clinical Fracture study). Since a different effect measure was used in Reid 2018, and also due to content issues, data deriving from this trial were looked at separately. A statistically significant effect in favour of the intervention was observed (p = 0.001).

The results tables and the forest plot on studies with enrichment design are presented below.

Table 5-14: Proportion of women with wrist fractures – Enrichment design

Study / Outcome definition	Treatment			Placebo			Treatment vs. Placebo		
	N	Women with wrist fractures		N	Women with wrist fractures		OR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT Clinical Fracture study [19]									
Wrist fractures	2,214	83	3.7	2,218	70	3.2	1.19[a]	[0.87; 1.64][a]	0.28[b]
FIT Vertebral Deformity study [20]									
Wrist fracture	1,022	22	2.2	1,005	41	4.1	0.52[c]	[0.31; 0.87][c]	ND
Reid 2018 [23]									
Wrist or forearm fracture	1,000	36	3.6[d]	1,000	63	6.3[d]	0.56[e]	[0.37; 0.85]	0.001

a: likelihood ratio method
b: log-rank test
c: proportional hazard model with likelihood ratio method
d: Rapid REA authors` own calculation
e: HR
Abbreviations: CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; OR: odds ratio; REA: relative effectiveness assessment

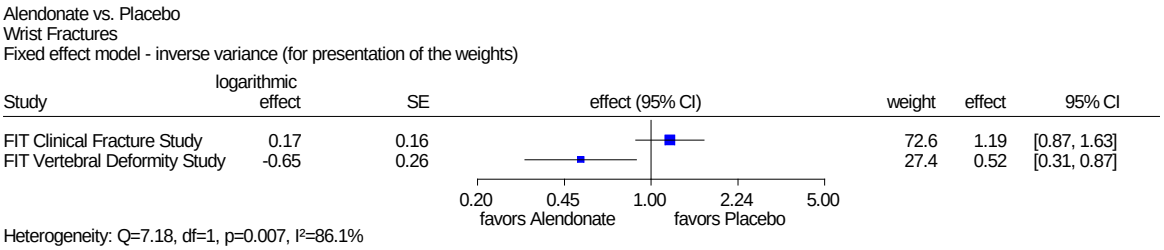

Figure 7: Forest plot on wrist fractures, effect measure: odds ratio – additional evidence

The quality of the evidence in the studies with enrichment design was downgraded to very low due to the overall high risk of bias and very serious indirectness due to an enrichment design.

Subgroup analyses

According to the specifications given in the Project Plan, the factors age, sex, BMI and ethnicity were to be examined for possible effect modification. In addition, it was checked whether it was possible to examine other factors, such as history of post-menopausal fractures and the influence of the calculated fracture risk, using a risk assessment tool with or without additional BMD measurement.

Subgroup analyses from strategy design studies were not available.

In a secondary analysis by Reid 2018 [29] the anti-fracture effect of zoledronic acid was investigated in subgroups. The analysis showed that the positive influence of zoledronic acid on the reduction of fractures was broadly consistent across the investigated cohort. There were no significant interactions between baseline variables (age, anthropometry, BMI, dietary calcium intake, baseline fracture status, recent falls history, BMD, and calculated fracture risk) and the treatment effect on fragility fractures. The operationalisation "fragility fractures" includes non-vertebral fractures as well as

morphometric vertebral fractures. About 11 % of the fractures were morphometric vertebral fractures. The evaluation can therefore be used to conclude that the baseline variables investigated may have little or no influence on the effectiveness of screening.

Conclusion on the quality of the evidence and on benefit statement regarding symptomatic fractures

The quality of the evidence ranked from high to low across the different fracture sub-outcomes in studies with marker-based strategy design. The limiting factor was mainly that heterogeneity was present with regard to the study designs and the results on hip fractures. In addition, some fracture outcomes were only reported in a single trial, so there was lack of replication. As data were available from strategy design studies in sufficiently high quality, the data from enrichment design studies were only presented as a supplement: Limiting factors in the additional study pool were mainly a high risk of bias and indirectness of results due to enrichment designs. Therefore, the quality of the evidence of results from enrichment design RCTs was rated as very low.

In summary, the quality of the evidence for the critical outcome "symptomatic fractures" can be assessed as moderate. In conclusion, screening for osteoporosis probably results in little or no difference in the incidence of symptomatic fractures compared with no screening.

The baseline variables investigated (age, anthropometry, BMI, dietary calcium intake, baseline fracture status, recent falls history, BMD, and calculated fracture risk) may have little or no influence on the effectiveness of screening. This conclusion is based on low-quality evidence.

[D0006] How does the screening for osteoporosis in the general population affect progression of the disease or health condition?

No follow-up measurements of BMD were made in the studies included. Therefore, this question cannot be answered due to a lack of data.

5.2.3.2 Back pain

[D0011] How does screening for osteoporosis affect body function? and

[D0016] How does the use of technology affect activities of daily living?

No data from studies with marker-based strategy design were available for the outcome "back pain".

Results from studies with enrichment design

In the Vertebral Deformity study of the FIT trial (women with pre-existing vertebral fractures [20]), the outcome was assessed in several operationalisations and the mean difference was estimated using change scores from baseline and follow-up scores [147]. Both the reduction in the number of bed-rest days due to back pain and the reduction in the number of limited activity days due to back pain were statistically significant in the intervention group ($p = 0.001$; $p = 0.04$, see Table 5-15). With regard to the final values, the number of bed-rest days also showed a statistically significant advantage in favour of the intervention group ($p = 0.002$ for ≥ 1 bed-rest days; $p < 0.001$ for ≥ 7 bed-rest days, see Table 5-16).

In Liang 2017 [21] no difference between intervention and control arm was observed with regard to back pain ($p = 0.919$, see Table 5-16).

The results tables on enrichment design studies are presented below.

Table 5-15: Number of days with back pain (change scores) – Enrichment design

Study / Outcome operationalisation	Treatment / Placebo	N[a]	Values at start of study Mean	Values at end of study Mean[b]	Changes compared to start of study[c]	Treatment vs. Placebo difference	Treatment vs. Placebo p value[d]
Enrichment design							
FIT (Vertebral Deformity study, [31]**)**							
No. of bed-rest days	Alendronate	1,022	1.3	1.9	ND	ND	0.001[e]
	Placebo	1,005	1.4	5.1	ND		
No. of limited activity days	Alendronate	1,022	21.3	61.8	ND	ND	0.04[e]
	Placebo	1,005	21.9	73.2	ND		
No. of days of moderate or worse pain	Alendronate	1,022	ND	185.6	ND	ND	0.53
	Placebo	1,005	ND	191.3	ND		
No. of days of severe or worse back pain	Alendronate	1,022	ND	32.4	ND	ND	0.07
	Placebo	1,005	ND	37.2	ND		

a: Number of persons to whom the evaluation refers

b: Number of days taken into account in the evaluation for calculating the effect estimator. The information on the end and start of the study (baseline) can be based on other patient numbers.

c: Unless otherwise stated, ITT-LOCF evaluation.

d: presumably from Wilcoxon test

e: comparison at end of study

Abbreviations: CI: confidence interval; LOCF: last observation carried forward; N: number of patients from ITT-population; ND: no data; No: number; SD: standard deviation

Table 5-16: Number of days with back pain (final values) – Enrichment design

Study / Outcome operationalisation	Treatment			Placebo			Treatment vs. Placebo		
	N	Women with back pain		N	Women with back pain		RR[a]	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT (Vertebral Deformity study, [31]**)**									
≥ 1 bed-rest days	1,022	114[b]	11.2	1,005	153[b]	15.2	0.68	[0.53; 0.87]	0.002
≥ 7 bed-rest days	1,022	43[b]	4.2	1,005	87[b]	8.7	0.44	[0.30; 0.64]	< 0.001
≥ 1 day(s) of severe or worse back pain	1,022	40[b]	3.9	1,005	53[b]	5.3	0.68	[0.45; 1.03]	0.07
≥ 7 limited-activity days	1,022	418[b]	40.9	1,005	442[b]	44.0	0.87	[0.76; 0.99]	0.06
≥ 7 moderate or worse back pain days	1,022	ND	ND	1,005	ND	ND	0.96	[0.86; 1.06]	ND
≥ 7 severe or worse back pain days	1,022	ND	ND	1,005	ND	ND	0.89	[0.74; 1.06]	ND
New or worsened disability	ND[c]	ND[d]	7.8	ND.[c]	ND.[d]	9.2	0.85	[0.63; 1.15]	0.29
Liang 2017 [21]									
Back pain	155	24	15.4	95	14	14.7	1.06 [b,e]	[0.52; 2.17][b]	0.919[b,f]

a: RR, CI: Proportional Hazard Model with likelihood ratio method, p value: log-rank test
b: Rapid REA authors` own calculation
c: Data were available for a total of 1843 persons (data for both study arms).
d: 156 (8.5%) of the persons had either new or worsened disability at the final visit
e: OR
f: unconditional exact method (CSZ-method [146])
Abbreviations: CI: confidence interval; N: number of patients evaluated; ND: no data; odds ratio, REA: relative effectiveness assessment; RR: relative risk; n: number of patients with event;

Conclusion on benefit regarding back pain

It is uncertain whether screening for osteoporosis improves back pain. The quality of the evidence was rated as very low. A limiting factor was that the results on back pain in the more informative trial were only reported for a subgroup (women with pre-existing vertebral fractures). However, as all data originated from studies with enrichment design and the results were inconclusive, the quality of the evidence was downgraded accordingly.

5.2.4 Health-related quality of life

[D0012] – What is the effect of screening for osteoporosis on generic health-related quality of life?

Results from RCTs with marker-based strategy design

HrQoL was investigated in the SCOOP trial [16]. In addition to EQ-5D, the SF-12 was used to evaluate mental and physical health. In the EQ-5D questionnaire and in both SF-12 questionnaires, no statistically significant difference between the 2 study arms was observed.

After 60 months of follow-up, the mean EQ-5D Score in the intervention group was 0.63 (SD: 0.33), while in the control group it was 0.63 (SD: 0.32, p = 0.154, between-group difference with repeated measures, ANOVA test). The estimated difference was calculated as -0.003, with adjustment for centre, age, and baseline EQ-5D Score (deaths imputed to zero).

After 60 months of follow-up, the mean SF-12 Score (physical health) in the intervention group was 38.3 (SD: 16.7), while in the control group it was 38.3 (SD: 16.6, p = 0.237, between-group difference with repeated measures, ANOVA test). The estimated difference was calculated as -0.20, with adjustment for centre, age, and baseline SF-12 Score (deaths imputed to zero).

After 60 months of follow-up, the mean SF-12 Score (mental health) in the intervention group was 46.0 (SD: 18.3), while in the control group it was 46.3 (SD: 18.2, p = 0.554, between-group difference with repeated measures, ANOVA test). The estimated difference was calculated as 0.56, with adjustment for centre, age, and baseline SF-12 Score (deaths imputed to zero).

Conclusion on the quality of the evidence and on health-related quality of life

Screening for osteoporosis probably results in little or no difference in HRQoL compared with no screening. This conclusion is based on moderate-quality evidence (downgraded by 1 level due to a high risk of bias).

5.2.5 Utilisation of healthcare resources

For this outcome, data were only available from the Vertebral Deformity study of the FIT trial.

Results from RCTs with enrichment design

In the Vertebral Deformity study of the FIT trial (women with pre-existing vertebral fractures [20]), fracture-related utilisation of healthcare resources was assessed in several operationalisations. In summary, 322 women experienced a clinical fracture, but only 192 of them experienced fracture-related healthcare utilisation. While there was no statistically significant difference for overall hospital stays or stays in nursing homes/rehabs (95 % CI for difference [-0.12; 0.21]; [-0.45; 0.23], respectively), the authors found a statistically significant reduction in the use of all resources and in the number of emergency room visits in favour of the intervention group (p = 0.038; p = 0.023, respectively).

The results table on studies with enrichment design is presented below.

Table 5-17: Proportion of women using healthcare resources – Enrichment design

Study / Outcome operationalisation	Treatment			Placebo			Treatment vs. Placebo		
	N	Women using healthcare resources		N	Women using healthcare resources		OR[a]	[95 % CI][a]	p value[a.b]
		n	%		n	%			
Enrichment design									
FIT Vertebral Deformity study [32]									
All resource use	1,022	109	10.8	1,005	83	8.1	0.73	[0.54; 0.98]	0.037
Emergency room	1,022	103	10.3	1,005	76	7.4	0.70	[0.52; 0.96]	0.026
Hospital stays	1,022	48	4.8	1,005	36	3.5	0.73	[0.47; 1.13]	0.164
Nursing homes/rehab	1,022	21	2.1	1,005	14	1.4	0.65	[0.33; 1.29]	0.248

a: Rapid REA authors` own calculation

b: unconditional exact method (CSZ-method [146])

Abbreviations: CI: confidence interval; n: number of patients with event; N: number of patients evaluated; OR: odds ratio; REA: relative effectiveness assessment

Conclusion on the quality of the evidence and on the utilisation of healthcare resources

It is uncertain whether screening for osteoporosis lowers fracture-related utilisation of healthcare resources. The quality of the evidence was rated as very low. A limiting factor was that results on back pain were only contributed by a subpopulation (women with pre-existing vertebral fractures, lack of replication in other trials). However, as all data originated from a study with enrichment design and the results were inconclusive, the quality of the evidence was downgraded accordingly.

[D0013] – What is the effect of screening for osteoporosis on generic disease-specific quality of life?

Data on anxiety were collected in the SCOOP trial [16]. However, since these data were not informative (no information available for the entire screening group), no conclusion could be drawn on the benefit or harm of screening compared with no screening for anxiety.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is screening for osteoporosis in relation to no screening?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the procedure of the screening process?

6.2 Results

6.2.1 Studies included

Since the answer to the safety domain also involves comparing the effects of a screening process with the effects of no screening, the same study pool (of RCTs) was used for the SAF domain as for the EFF domain.

6.2.2 Patient safety

[C0008] - How safe is screening for osteoporosis in relation to no screening?

Data on (serious) adverse events were not or not adequately assessed in the studies with marker-based strategy design. While this outcome was not reported at all in ROSE and COSHIBA, in SCOOP “GPs were [only] asked to record any adverse events related to the screening process” [16].

Results on RCTs with enrichment design

(Serious) adverse events were assessed in the 2 sub-studies of the FIT trial, in Reid 2018 and in Liang 2017.

In the FIT sub-trials, alendronate was administered in the form of a daily tablet. Where possible, the effects of the Clinical Fracture study and the Vertebral Deformity study were considered together. Since in Reid 2018 and in Liang 2017, zoledronic acid was administered (given once every 18 months and once per year intravenously, respectively) and the length of follow-up also differed from the follow-up in the FIT trial (6 and 2 years, respectively), the results are considered separately in the following text.

An overall rate for adverse events was reported neither in the FIT studies nor in Liang 2017. The following sections include a brief overview of the most common and most serious adverse events.

Alendronate

A statistically significant difference regarding adverse events resulting in hospital admission was found in the Vertebral Deformity study of the FIT trial [20]. However, the results on this operationalisation were regarded to be less relevant, since they also included hospitalisations due to fracture and were inconsistent between the 2 sub-studies of the FIT trial. In the Vertebral Deformity study, patients were followed for a mean of 2.9 years. Looking at both FIT trials together, similar proportions of women in the 2 groups permanently discontinued study medication because of adverse events due to upper gastrointestinal tract symptoms (7.6 % alendronate versus 9.6 % placebo; p = 0.123) [33].

Similar rates were reported for upper gastrointestinal tract symptoms or events (47.5 % in the alendronate group and 46.2 % in the placebo group), as well as gastric or duodenal perforations, ulcers

and bleeding, and oesophageal and serious oesophageal events [33]. The same applied to the rates for (severe) atrial fibrillation [34].

Zoledronic acid

In Reid 2018, zoledronic acid was administered in 18-month intervals and follow-up was 6 years. The overall rate of serious adverse events showed an advantage for the intervention group, which was marginally not statistically significant and included fractures that resulted in hospitalisation. An overall rate for adverse events was not reported. No statistically significant differences in other (serious) adverse events were observed. Frequently expected adverse effects that may occur after administration of intravenous zoledronic acid, such as flu-like symptoms, headache or gastrointestinal symptoms, were not among the pre-specified adverse effects and were not reported. Differences to the advantage of the intervention group were reported for melanoma skin cancers. However, this outcome was not one of the pre-specified outcomes and should be interpreted with caution against the background of multiple testing.

No serious adverse events occurred in Liang 2017 [21] within the follow-up of 2 years. Adverse events were only reported if they occurred within 3 days after drug administration and in more than 5 % of patients. The quality of information was therefore limited. An overall rate of adverse events was not reported. The effect on unspecific adverse events such as influenza-like illness, pyrexia and myalgia was large and occurred significantly more often in the intervention group than in the control group ($p = 0.003$, $p < 0.001$, and $p < 0.001$). It was stated that “the most common post-dose symptom adverse events were generally mild to moderate in intensity and were of short duration (the majority lasting 3 days or less)”.

The results table on studies with enrichment design is presented below.

Table 6-1: Proportion of women with (serious) adverse events and risk assessment – Enrichment design

Study / drug Outcome operationalisation	Treatment			Placebo			Treatment vs. Placebo		
	N	Women with (S)AEs		N	Women with (S)AEs		RR	[95 % CI]	p value
		n	%		n	%			
Enrichment design									
FIT Clinical Fracture study [19] - Alendronate									
Any leading to hospitalisation	2,214	644	29.1	2,218	596	26.9	1.09[a]	[0.98; 1.22][b]	ND
FIT Vertebral Deformity study [20] - Alendronate									
Adverse events resulting in hospital admission	1,022	250	24.5	1,005	300	29.9	ND	ND	0.009
FIT (pooled data from both Clinical Fracture study and Vertebral Deformity study) [33,34] - Alendronate									
Upper GI tract symptoms or events	3,236	1,536	47.5	3,223	1,490	46.2	1.02	[0.95; 1.10][c]	0.46[d]
Discontinuation of study medication due to upper GI tract symptoms	3,236	102	3.2	3,223	88	2.7	1.15	[0.87; 1.54][c]	ND
Any gastric or duodenal PUBs	3,236	53	1.6	3,223	61	1.9	0.86	[0.59; 1.24][c]	0.42[c]
Oesophageal events	3,236	322	10.0	3,223	303	9.4	1.06	[0,91; 1,24][c]	0,45[d]
Serious oesophageal events	3,236	10	0.3	3,223	6	0.2	2.19	[0.80; 6.95][c]	ND
Atrial fibrillation	3,236	81	2.5	3,223	71	2.2	1.14[e]	[0.83; 1.57]	0.42
Serious atrial fibrillation	3,236	47	1.5	3,223	31	1.0	1.51[e]	[0.97; 2.40]	0.07
Liang 2017 [21] – Zoledronic acid									
SAEs[f]	175	0	0	110	0	0	--	--	--
Headache (influenza-like illness)[g]	155	21	13.5	95	2	2.1	0.729[h, i]	[1.67; 31.38][i]	0.003[i, j]
Pyrexia[g]	155	43	27.7	95	3	3.2	11.77[h, i]	[3.45; 39.19][i]	< 0.001[i,j]
Myalgia[g]	155	34	21.9	95	4	4.2	6.39[h, i]	[2.19; 18.66][i]	< 0.001[i,j]
Arthralgia[g]	155	29	18.7	95	11	11.6	1.79[h,i]	[0.85; 3.74][i]	0.144[i,j]

Study / drug Outcome operationalisation	Treatment N	Treatment Women with (S)AEs n	Treatment Women with (S)AEs %	Placebo N	Placebo Women with (S)AEs n	Placebo Women with (S)AEs %	Treatment vs. Placebo RR	Treatment vs. Placebo [95 % CI]	Treatment vs. Placebo p value
Reid 2018 [23] – Zoledronic acid									
SAEs[k]	1,000	400	40[i]	1,000	443	44[i]	0.84[h]	[0.70; 1.00]	ND
Sudden death	1,000	1	0.1[i]	1,000	1	0.1[i]	3.01[h]	[0.3; 28.9]	ND
Myocardial infarction	1,000	24	2.4[i]	1,000	39	3.9[i]	0.61[h]	[0.36; 1.02]	ND
Coronary-artery revascularization	1,000	21	2.1[i]	1,000	30	3.0[i]	0.72[h]	[0.41; 1,27]	ND
Stroke	1,000	17	1.7[i]	1,000	20	2.0[i]	0.85[h]	[0.44; 1.63]	ND
Composite of vascular events[l]	1,000	53	5.3[i]	1,000	69	6.9[i]	0.76[h]	[0.52; 1.09]	ND
Transient ischemic attack	1,000	23	2.3[i]	1,000	14	1.4[i]	1.66[h]	[0.85; 3.24]	ND
Cancer[m,n]	1,000	84	8.4[i]	1,000	121	1.2[i]	0.67[h]	[0.50; 0.89]	ND
Osteonecrosis of the jaw	1,000	0	0	1,000	0	0	--	--	--
Atrial fibrillation	1,000	54	5.4[i]	1,000	55	5.5[i]	0.98[h]	[0.67; 1.44]	ND

a: HR
b: likelihood ratio method
c: Proportional Hazard Model
d: log-rank test for differences in cumulative incidence curves
e: described as “relative hazard”, interpreted as HR
f: such as osteonecrosis of the jaw, atrial fibrillation, ocular inflammation, symptomatic hypocalcaemia
g: events occurred in > 5 % of patients within 3 days after drug admission
h: OR
i: Rapid REA authors` own calculation
j: unconditional exact method (CSZ-method [146])
k: included fractures that resulted in hospitalisation
l: sudden death, myocardial infarction, coronary-artery revascularisation, or stroke
m: excluded non-melanoma skin cancers
n: only cancer in general was pre-specified in the study protocol
Abbreviations: CI: confidence interval; GI: gastrointestinal; HR: hazard ratio; n: number of patients with event; N: number of patients evaluated; ND: no data; OR: odds ratio; PUB: perforation, ulcers, and bleeding; REA: relative effectiveness assessment; RR: relative risk; SAEs: serious adverse events

Conclusion on the quality of the evidence and on (serious) adverse events

As only data from enrichment design studies could be used to assess adverse events of screening for osteoporosis, the quality of the evidence was downgraded by 2 levels due to indirectness. Since additionally the risk of bias was high in the study pool investigating alendronate, the quality of the evidence was consequently rated as “very low”. In the FIT trials a statistically significant difference was found for adverse events resulting in hospitalisation. However, this also included hospitalisation due to fracture. Due to the very low quality of the evidence, it is uncertain to what extent side effects occur if alendronate forms part of the screening-treatment strategy.

The quality of the evidence deriving from Reid 2018 was rated as low. Thus, it was possible to draw a conclusion on benefit or harm for the outcome “serious adverse events” if zoledronic acid forms part of the screening approach. Data from Reid 2018 suggest that screening for osteoporosis in postmenopausal women may result in little or no difference in the rate of serious adverse events if zoledronic acid (administered intravenously in 18-month intervals) forms part of the screening-treatment strategy. Data on short-term adverse events were reported by Liang 2017. However, these were only assessed in a timeframe of 3 days after drug administration and only if they occurred in more than 5 % of the participants. Although the observed effects were very large, the risk of bias was high and the ITT principle was not adequately implemented, which is why the extent of short-term adverse events is uncertain if zoledronic acid forms part of the screening-treatment strategy.

Overdiagnosis

An estimation of the frequency or proportion of overdiagnoses caused by osteoporosis screening was not possible, as no data were found on this outcome.

[C0002] – Are the harms related to dosage or frequency of applying the technology?

The influence of screening intervals was not investigated in the studies included. A statement as to whether harm is potentially related to a certain screening interval is therefore not possible.

[C0004] – How does the frequency or severity of harms change over time or in different settings?

Based on the available studies, no reliable conclusion is possible on whether (serious) adverse events occur with the screening-treatment strategy used, nor is a conclusion possible on the frequency or severity of harms in connection with the number of screening intervals or with different settings.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the procedure of the screening process?

In all studies included only postmenopausal women were examined. Therefore, with regard to potential harms, it was not possible to assess whether – compared with postmenopausal women – men or younger women have a higher or a lower risk of adverse events. The studies included failed to describe whether specific subgroups of postmenopausal women had a higher risk of adverse events.

For information on further subgroup analyses, see the answers given in [D0005].

7 PATIENT INVOLVEMENT

The development of the present Rapid REA was supported by the input of patients with primary osteoporosis. At the beginning of the evaluation, 2 large German patient organisations were contacted in order to identify patients with primary osteoporosis. As a result, 3 female patients completed a questionnaire, which asked open questions about aspects of the disease and its treatment. Thus, the patients had the opportunity to comment on their experience with the disease and provide an opinion on whether certain patient groups should be given particular consideration. In addition, they were asked to describe their experience with the previous treatment and their expectations of new therapies.

A final section offered the opportunity to comment freely on the subject. The English translation of the questionnaire is presented in Section 10.1.3 in Appendix 1.

The responses were used to raise awareness of additional patient-relevant outcomes. No additional relevant outcomes were identified. Fractures and associated pain were frequently mentioned by all patients. Since the focus of most of the studies included was also on the incidence of symptomatic fractures, this outcome was classified as "critical" for the present assessment.

8 DISCUSSION

The main finding of the present Rapid REA was that screening for osteoporosis in postmenopausal women probably has little or no effect on the incidence of symptomatic fractures (covering all clinical fractures that presumably were experienced as symptomatic by the patient). This finding was mainly based on 3 large screening RCTs (ROSE, SCOOP, and COSHIBA), which all employed the "conventional" study design of comparing a screen-and-treat strategy with no screening. Further but much weaker evidence came from 5 RCTs using an enrichment design. For the outcomes symptomatic fractures, back pain, utilisation of healthcare resources, HrQoL, and mortality, no difference between screening and no screening was observed. The outcome symptomatic fractures consisted of several sub-outcomes. While there was no difference between the study arms in any of the composite fracture outcomes investigated, the effects on hip fractures were heterogeneous (and statistically significant in the SCOOP trial); for wrist fractures, a marginally statistically significant benefit was found in the single study (COSHIBA) reporting this outcome. However, the event rates were low and no other strategy design RCT reported data to reproduce this finding. Back pain and utilisation of healthcare resources were not reported in strategy design RCTs. Therefore, only results from enrichment design studies could be used. However, due to very low quality, the evidence was too weak to adequately evaluate both outcomes. In this Rapid REA, enrichment design studies were mainly consulted in order to determine the extent of possible expected harm deriving from a screening approach that contains anti-osteoporosis drug treatment. In 1 study investigating zoledronic acid (Reid 2018), no difference between intervention and control arm was observed regarding serious adverse events. No conclusion could be drawn from the 2 other RCTs on zoledronic acid (Liang 2017 and Yang 2015) with regard to the extent of serious adverse events and short-term adverse events due to their very low quality of evidence. For the same reason, no conclusion could be drawn if alendronate formed part of the screening approach. Future screening RCTs should collect data on (serious) adverse events, even though the adverse effects of most drugs are well known.

Since strategy design studies investigate the entire screening-treatment approach, their results are highly valid in assessing the real-world effectiveness of screening. In the present studies, between one and two thirds of the women participated in screening, and a better participation rate is not to be expected in routine care. It should also be noted that the women who took part in the screening tests were younger, healthier, better educated, and socioeconomically better off than those who did not. This is also to be expected in population-based screening ("healthy volunteer bias" [16,91]). Nevertheless, it is possible that strategy design studies underestimate effects. A potential problem of the screening studies included is contamination bias, which means that women in the control group might have become aware of their osteoporosis and then actively sought testing for the disease. The 2 study arms thus would have become more similar, so that differences between arms would probably have been underestimated. The effectiveness of screening for osteoporosis depends heavily on the exact screening-treatment strategy and the healthcare context. Since in all strategy design RCTs the women in the control group were each asked to fill in a questionnaire that captured fracture risk factors, it can be assumed that the setting of the 2 studies can only be applied to the real-world context to a limited extent.

Studies with enrichment design have mainly been included in this Rapid REA because it was assumed that strategy design studies would not adequately report possible (serious) adverse effects. For pragmatic reasons, only enrichment design studies limited to anti-osteoporosis drug treatment were included in this report. Further therapy options (e.g. prevention of falls, nutrition management) as well as further triggers for adverse events, such as overdiagnosis or a false-negative screening result, could not be and are not covered by studies of this design and research question. It is known that adverse events related to anti-osteoporosis drugs can occur and vary in frequency and severity

depending on both the drug itself (the active ingredient) and the duration of use [126]. Although the enrichment design studies included were required to have recruited study participants from the general population, they are severely hampered by their serious indirectness. On the one hand, there might be differences in the population. While FRAX and DXA were used in the 2 large strategy design studies to assess fracture risk, patients were mainly included in the enrichment design studies only via BMD measurement. However, it is unclear to what extent the populations with high fracture risk differ from those with low bone density. In addition, studies with enrichment design answer a narrower research question than studies with strategy design, namely, whether it is beneficial to treat test-positive patients. This leads to the following differences: Firstly, patients who are included in an enrichment design RCT usually represent a positive selection, so their adherence and results may be higher than those of average patients. In a drug trial, it is even possible that patients receive remuneration for their participation. Secondly, especially participants of the 2 FIT trials represent a highly selected sample, as the adapted exclusion criteria go far beyond those needed for the prescription of an anti-osteoporosis drug. In addition, enrichment design RCTs deliver no results on test-negative persons or on persons who declined further testing or treatment. Even if one assumes neither positive nor negative consequences in these persons, the effect of treatment is potentially artificially enhanced in an enrichment design. Therefore, these studies tend to show larger positive (but also negative) effects than strategy design studies. However, regarding the research question of the present Rapid REA, the results from enrichment design RCTs must be viewed as clearly less valid, which is why downgrading them 2 steps due to serious indirectness seems appropriate.

Within the framework of the national uptake of osteoporosis screening in European countries, observational data could be used to consider more specific population groups in the event of a positive result. The conclusions of the present REA are based on data of the highest evidence level, so they should not be changed by lower-quality data from observational studies.

External validity

Only postmenopausal women were investigated in the studies included. This is understandable because postmenopausal women form the group of people with the highest prevalence of osteoporosis [1]. However, this means that no conclusion can be drawn regarding the benefit or harm of osteoporosis screening in younger women and in men.

The FRAX tool is the risk assessment tool that has probably been most extensively investigated; this tool takes mortality into account as a competing risk and has been adapted for 64 countries [4]. The risk of fractures differs markedly in Europe [1,7,144] and FRAX is calibrated to those countries where the epidemiology of fracture and mortality is known [1]. Treatment thresholds vary in the different countries. They can be fixed (based on a fixed risk of fracture or on cost-effectiveness analyses), age-dependent, or both. While Kanis states that the country-specific fracture risk at which treatment is recommended varies little in the Western world [144], the EU standardised fracture incidence seems to vary markedly between different EU countries [7]. The country-specific FRAX algorithms are not freely accessible and it is therefore unclear how much the various FRAX models differ and whether the risk profiles (and therefore probably the treatment responses) of patients will vary depending on these adaptations or not. Against this background, it is unclear whether different FRAX algorithms are able to identify sufficiently similar patients.

In addition, the drug treatment after test-positive screening was only described for the ROSE trial [35], while in both SCOOP and ROSE no information was available regarding non-drug anti-osteoporosis interventions. Treatment decisions were up to the GPs and were not pre-specified in the study protocols. However, non-drug anti-osteoporosis management is also recommended in current guidelines [1,104,141] and may have a relevant influence on fracture occurrence [148-153]. Thus,

it is ultimately uncertain whether, and if yes, to what degree, treatment was comparable between the studies. Despite the uncertainties described above, the findings of the Rapid REA are in principle considered applicable to the European context but presumably not to alternative screening strategies.

Interpretation of hip fracture findings

Although the 2 large screening RCTs in this Rapid REA investigate a very similar screening approach (FRAX + subsequent DXA), they differ in their study design: In ROSE, the potential participants were randomised before the invitation to screening. Thus, the entire screening-treatment strategy, including the invitation process, was investigated. In SCOOP, the participants were randomised only after signing the consent form, so that a certain selection, for example by the GPs, had already taken place before randomisation. It seems possible that this difference explains the different results on hip fractures. The difference may be interpreted as meaning that optimising the invitation process increases acceptance and thus also improves the participation rate. More people with an increased risk of fractures might then participate and further fractures might be prevented.

Overdiagnoses

A particular aspect of harm from screening is overdiagnosis. An overdiagnosis is defined as a correct diagnosis of a disease, which – without screening - would not have been noticed and would not have caused any symptoms such as back pain or fractures during the patient's lifetime. Overdiagnosis occurs in particular when screening focuses on a slowly progressive disease or on an elderly population, as both factors increase the likelihood that an unrelated death occurs before the disease causes symptoms. Overdiagnosis and subsequently overtreatment can neither be avoided nor detected directly. However, it can be suspected that overdiagnosis and the associated overtreatments pose a relevant risk. Although a diagnosis of osteoporosis may motivate a healthier lifestyle, it may also lead to limitations, because the person affected could restrict his or her everyday life in order to avoid falls. In addition, a feeling of weakness and fragility may occur and the diagnosis itself may lead to stigmatisation. A possible way to address this problem could therefore be to understand and communicate osteoporosis not as a "disease" but as a risk factor for fractures [154].

An estimation of the frequency or proportion of overdiagnoses caused by osteoporosis screening was not possible, as no data were found in the studies included. No further publications estimating the proportion of overdiagnosis were identified.

While there is great concern that osteoporosis is underdiagnosed and thus undertreated [155], other opinions exist. Critics of osteoporosis screening state that fractures are closely linked to old age and most fractures occur in people without osteoporosis [140,156]. They also state that consequently a large number of healthy people are treated without experiencing a relevant benefit, as widely used anti-osteoporosis drugs show only small absolute reductions in fracture risk [140,154,157] (175 women must be treated for 3 years to prevent 1 hip fracture [140]). They note that osteoporosis drugs can have significant adverse effects, although this was hardly investigated in the studies included in this Rapid REA. They thus question the use of drug treatment as the main treatment approach, as it shifts the focus from non-drug approaches, which may have a greater impact on fracture rates and fewer adverse effects [140].

Radiation aspects

BMD measurement with DXA results in radiation exposure from 0.2 to 15 µSV [158]; the measurement lasts 5 to 10 minutes. Radiation exposure is thus lower than the average annual exposure to

earth radiation (2.4 mSv per year [159]) and is assumed to be almost negligible as a single procedure [160]. However, an assessment of potential harm from radiation exposure could not be made on the basis of the studies included.

Publication bias

A strategy design RCT without published results was identified which, according to the corresponding publication on the protocol, should already have been completed (POROS [27]). No registry entry could be identified for this study, and an author enquiry about the currently unclear status of the study was not answered. This situation is concerning because of possible publication bias. The funnel plot method could not be applied due to the small overall number of trials. However, as the potentially missing study only accounts for about 5 % of the total population included, the influence of publication bias was not considered to be relevant.

The second study without published results, also a strategy design RCT, was the SALT study, which can currently be classified as "ongoing"[4].

Critical reflexion of the approach of the present Rapid REA

Inclusion and handling of composite fracture outcomes

The single event rates of the components of the composite fracture outcomes were not regularly reported in the publications and were not provided by the authors on request. Nevertheless, these composite fracture outcomes were accepted in this Rapid REA. The following reasons are based on the EUnetHTA guideline “Endpoints used for Relative Effectiveness Assessment – Composite endpoints”:

Firstly, it could be assumed that the severity of the outcome components was sufficiently comparable, as fractures at different sites were combined into a composite outcome. Secondly, objective and subjective outcomes were not combined. In most studies, the fracture events were documented by x-rays and / or doctors' letters. Patient-reported and clinician-reported events were therefore not combined into a composite outcome.

In this Rapid REA, composite fracture outcomes were quantitatively summarised whenever possible and meaningful. This was done even though the components were not always completely identical. However, the severity of the components was deemed to be comparable and in addition, the fracture groups were considered to be sufficiently similar. A possible multiplicity problem did not arise due to the lack of statistical significance of the results on the individual sub-outcomes across studies.

This Rapid REA compared with other systematic reviews and guidelines

The 2 most recent guidelines on osteoporosis are the European guideline by Kanis et al. and the recommendations of the USPSTF, published in 2019 and 2018, respectively. Both guidelines were able to include at least SCOOP in their assessment as an important conventional screening study.

The European guideline states that there is no uniformly accepted policy for population-based screening in Europe: currently patients are mostly identified by opportunistic screening - based either on fragility fractures or in the presence of other risk factors. Nevertheless, the utility of age-dependent FRAX thresholds in the population-based screening approach is described as being feasible, effective and health-economically viable. The guideline does not address men [1].

[4] The results of this study were published after our update search in May 2019 and could therefore not be included in this Rapid REA. Future assessments should take the results into account.

The USPSTF recommends screening for osteoporosis using BMD to prevent fractures for women of 65 years and older and for postmenopausal women under 65 who are at increased risk. For men, “the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures” [109].

The SR that forms the basis of the USPSTF recommendations was prepared by the AHRQ [14]. It was identified in the focused search and formed a data basis for the present Rapid REA, since the main question of the AHRQ report was whether screening for osteoporosis in the general population using a clinical risk assessment tool and / or bone density measurement has a relevant influence on the reduction of osteoporosis-associated morbidity and mortality in adults. Therefore, the aim of the AHRQ report was expected to be very similar to the research question investigated in the present Rapid REA and the main inclusion criteria were also similar. Nevertheless, the authors of the AHRQ review adopted a slightly different approach: In further research questions the accuracy and reliability of screening approaches were investigated and the benefit and harm of drug therapy in osteoporosis was investigated separately. The populations in the screening-treatment and treatment-only studies differed in their predefined inclusion criteria. Thus, as in the present Rapid REA, no linked evidence approach was chosen, but the questions were answered individually. Although the AHRQ report identified treatment studies that screened individuals from the general population, these studies were not used to support a conclusion on the benefit or harm of the screening approach. As a result, a benefit for different drugs could be derived with regard to patient-relevant outcomes. However, the authors only drew conclusions as to whether screening in the general population could result in a benefit or harm with regard to patient-relevant outcomes on the basis of 1 study on the entire screening-treatment process in postmenopausal women between 70 to 85 years (SCOOP). The results indicated a reduction in hip fractures, but potential harms of the entire screening-treatment process were not investigated [1,109].

Summary of limitations of the Rapid REA

Firstly, this Rapid REA focused on drug treatment options. Strategy design studies in which non-drug treatment options were offered to test-positive patients were searched for, but not found. With regard to enrichment design studies, literature searches did not address other or additional treatment options such as preventive measures for falls, nutrition and lifestyle recommendations, exercise or physical therapy, vitamin supplementation or household safety improvements, which might also effectively reduce the risk of fractures [148-153]. This was done for pragmatic reasons, as drug treatment is described as the main component of anti-osteoporosis measures in current guidelines. Secondly, the studies were not homogeneous in terms of their inclusion criteria and screening approach. In 1 of the 3 strategy design RCTs, no BMD measurement was performed (COSHIBA) and it is uncertain to what extent the population from the strategy design studies (identified via FRAX and BMD measurement) was similar to the population from the enrichment design studies (identified via BMD measurement). Thirdly, the evidence was sparse or even lacking with respect to other screening approaches (e.g. using other risk assessment tools such as qUS or qCT) and screening in younger women and men.

Perspective

The studies included showed no effect of screening. However, it was notable that the results on hip fractures were inconclusive. It should thus be noted that the results cannot be interpreted as proof of no benefit. Since some potentially dilutive effects may have been present (invitation procedure, risk assessment of the control group), it cannot be ruled out that an improved screening-treatment strategy might deliver other, positive results. When designing future studies, it would be important to ensure that a more stringent (but at the same time implementable) screen-and-treat approach is developed, so that weaknesses in study design resulting in low participation and treatment adherence rates are avoided.

The results of the SALT study (n = 11,032 participants) were published after the Rapid REA`s editorial deadline on 13 May 2019 [161]. They could therefore not be considered in this report. However, there was no statistically significant effect on fractures of any type, falls, or mortality. These results should be included in future assessments.

9 CONCLUSION

Since the available studies of moderate quality show no effect of screening on the incidence of symptomatic fractures, screening for osteoporosis in postmenopausal women probably has little or no benefit. These findings are mainly based on studies investigating a screening strategy using FRAX for risk assessment and DXA for BMD measurement. The studies included did not allow the evaluation of screening strategies based on other screening tools. As in any screening intervention, benefits and harms are affected by multiple factors such as the type and uptake of screening and treatment. No studies were found on osteoporosis screening in men or younger women.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

Documentation of the search strategies

Focused search for SRs / HTAs

1. MEDLINE

Search Interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2018
- Ovid MEDLINE(R) 1946 to July Week 1 2018
- Ovid MEDLINE(R) Daily Update July 11, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 11, 2018

The following filters were adopted:

- Systemtic Review: Wong [162] – High specificity strategy

#	Searches
1	(osteoporosis or osteoporotic).mp.
2	(fracture* or (bone adj3 density)).ti.
3	or/1-2
4	(screening* or screened* or "case finding").mp.
5	Cochrane database of systematic reviews.jn.
6	(search or MEDLINE or systematic review).tw.
7	meta analysis.pt.
8	or/5-7
9	and/3-4,8
10	..l/ 9 yr=2013-Current

2. PubMed

Search Interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (osteoporosis OR osteoporotic)
#2	Search (fracture*[TI] OR bone density[TI])
#3	Search (#1 OR #2)
#4	Search (screening* or screened* or "case finding")
#5	Search (search[TIAB] OR meta analysis[TIAB] OR MEDLINE[TIAB] OR systematic review[TIAB])
#6	Search (#3 AND #4 AND #5)
#7	Search (#6 NOT Medline [SB])
#8	Search (#7 AND 2013:2018 [DP])

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews : Issue 7 of 12, July 2018

ID	Search
#1	[mh Osteoporosis]
#2	(osteoporosis or osteoporotic):ab,ti
#3	(fracture* or (bone near/3 density)):ti
#4	#1 or #2 or #3
#5	(screening* or screened* or "case finding"):ab,ti
#6	#4 and #5 Publication Year from 2013 to 2018, in Cochrane Reviews (Reviews and Protocols)

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	(osteoporosis or osteoporotic)
2	(fracture*)
3	(bone AND density)
4	(#1 OR #2 OR #3)
5	(screening* or screened* or "case finding")
6	(#4 AND #5)
7	((#6) FROM 2013 TO 2018)
8	((#7) IN HTA)

Comprehensive search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to May 10, 2019

Marker-based strategy design

The following filters were adopted:

RCT: Lefebvre [163] – Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	exp Osteoporosis/
2	exp *Fractures, Bone/
3	Bone Density/
4	(osteoporosis or osteoporotic).ti,ab.
5	fracture*.ti.
6	(bone* adj3 (densit* or loss* or mass*)).ti.
7	or/1-6
8	screen*.mp.
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.

#	Searches
11	(randomized or placebo or randomly or trial or groups).ab.
12	drug therapy.fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	and/7-8,14
16	..l/ 15 yr=2016-Current
17	16 not (comment or editorial).pt.

Enrichment design

The following filters were adopted:

RCT: Lefebvre [163] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	exp Osteoporosis/
2	exp *Fractures, Bone/
3	Bone Density/
4	(osteoporosis or osteoporotic).ti,ab.
5	fracture*.ti.
6	(bone* adj3 (densit* or loss* or mass*)).ti.
7	or/1-6
8	(raloxifen* or bazedoxifen* or alendronat* or risedronic* or risedronat* or ibandronat* or ibandronic* or zoledronic* or zoledronat* or parathyroid hormon* or teriparatid* or strontium ranelat* or denosumab*).mp.
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly).ab.
12	clinical trials as topic.sh.
13	trial.ti.
14	or/9-13
15	14 not (exp animals/ not humans.sh.)
16	and/7-8,15
17	16 not (comment or editorial).pt.
18	..l/ 17 yr=2016-Current

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (osteoporosis [TIAB] OR osteoporotic [TIAB])
#2	Search fracture*[TI]
#3	Search (bone*[TI] AND (densit*[TI] or loss*[TI] or mass*[TI]))
#4	Search (#1 OR #2 OR #3)
#5	Search (screening* [TIAB] OR screened* [TIAB])
#6	Search ((raloxifene or bazedoxifene or alendronate or risedronic or risedronate or ibandronate or ibandronic or zoledronic or zoledronate or parathyroid hormone or teriparatide or strontium ranelate or denosumab))
#7	Search (clinical trial*[TIAB] OR random*[TIAB] OR placebo[TIAB] OR trial[TI])
#8	Search (#4 AND (#5 OR #6) AND #7)
#9	Search (#8 NOT Medline [SB])
#10	Search (#9 AND 2016:2018 [DP])

3. Embase

Search interface: Ovid

Embase 1974 to 2019 May 10

The following filters were adopted:

RCT: Wong [162] – Strategy minimising difference between sensitivity and specificity

#	Searches
1	exp Osteoporosis/
2	exp *Fracture/
3	*Bone Density/
4	(osteoporosis or osteoporotic).ti,ab.
5	fracture*.ti.
6	(bone* adj3 (densit* or loss* or mass*)).ti.
7	or/1-6
8	screen*.mp.
9	(raloxifen* or bazedoxifen* or alendronat* or risedronic* or risedronat* or ibandronat* or iband-ronic* or zoledronic* or zoledronat* or parathyroid hormon* or teriparatid* or strontium ranelat* or denosumab*).mp.
10	or/8-9
11	(random* or double-blind*).tw.
12	placebo*.mp.
13	or/11-12
14	and/7,10,13
15	14 not medline.cr.
16	exp animal/ not exp human/
17	15 not 16

#	Searches
18	17 not (Conference Abstract or Conference Review or Editorial).pt.
19	..l/ 18 yr=2016-Current

4. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 5 of 12, May 2019

ID	Search
#1	[mh "Osteoporosis"]
#2	[mh "Fractures, Bone"[mj]]
#3	[mh "Bone Density"]
#4	(osteoporosis or osteoporotic):ti,ab
#5	fracture*:ti
#6	(bone* NEAR/3 (densit* or loss* or mass*)).ti
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	screen*
#9	(raloxifen* or bazedoxifen* or alendronat* or risedronic* or risedronat* or ibandronat* or iband-ronic* or zoledronic* or zoledronat* or parathyroid hormon* or teriparatid* or strontium ranelat* or denosumab*):ab,ti,kw
#10	#7 and (#8 OR #9) with Cochrane Library publication date Between Jan 2016 and Dec 2018, in Trials

Search in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov

Input surface: Expert Search

Search strategy
(osteoporosis OR osteoporotic) [DISEASE] AND (screening OR raloxifene OR bazedoxifene OR alen-dronate OR risedronic OR risedronate OR ibandronate OR ibandronic OR zoledronic OR zoledronate OR parathyroid hormone OR teriparatide OR strontium ranelate OR denosumab) [TREATMENT]

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search

Input surface: Basic Search

Search strategy
(osteoporosis OR osteoporotic) AND (raloxifene OR (LY 139481) OR LY139481 OR (LY 156758) OR LY156758 OR bazedoxifene OR (TSE 424) OR TSE424 OR alendronate OR (MK 217) OR MK217 OR risedronic OR risedronate OR (NE 58095) OR NE58095 OR ibandronate OR ibandronic OR zoledronic OR zoledronate OR (ZOL 446) OR ZOL446 OR (CGP 42446) OR CGP42446 OR parathyroid hormone OR (ALX1 11) OR ALX111 OR teriparatide OR (LY 333334) OR LY333334 OR (strontium ranelate) OR (s 12911) OR s12911 OR denosumab OR (AMG 162) OR AMG162)

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/

Input surface: Advanced Search

Search strategy
osteoporosis OR osteoporotic in the Condition AND screen* OR raloxifene OR LY 139481 OR LY139481 OR LY 156758 OR LY156758 OR bazedoxifene OR TSE 424 OR TSE424 OR alendronate OR MK 217 OR MK217 OR risedronic OR risedronate OR NE 58095 OR NE58095 OR ibandronate OR ibandronic in the Intervention Recruitment status is ALL
osteoporosis OR osteoporotic in the Condition AND zoledronic OR zoledronate OR ZOL 446 OR ZOL446 OR CGP 42446 OR CGP42446 OR parathyroid hormone OR ALX1 11 OR ALX111 OR teriparatide OR LY 333334 OR LY333334 OR strontium ranelate OR s 12911 OR s12911 OR denosumab OR AMG 162 OR AMG162 in the Intervention " Recruitment status is ALL
Screen* in the Title AND osteoporosis OR osteoporotic in the Condition Recruitment status is ALL

List of excluded documents with reasons for exclusion

Not I1: Population

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5. Beekman KM, Veldhuis-Vlug AG, Den Heijer M, Maas M, Oleksik AM, Tanck MW et al. The effect of raloxifene on bone marrow adipose tissue and bone turnover in postmenopausal women with osteoporosis. Bone 11.10.2017 [Epub ahead of print].

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Not I2: Intervention

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Not I4: Outcome

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Not I5: Study design

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Not I6: Type of publication

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Assessment of the information retrieval of the systematic reviews included

Table A-1: Quality assessment of the SRs included

Viswanathan, 2018 [14]	**Yes / No / N.A.**	**Explanations**
1. Were at least 2 different types of information sources searched (e.g. bibliographic databases and study registries)? Please list all types of information sources reported.	Yes	1. Bibliographic databases 2. Study registries (target search) 3. Drugs@FDA.gov 4. Reference lists
2. Were at least 2 different bibliographic databases searched? Please list all bibliographic databases reported.	Yes	PubMed, the Cochrane Library and Embase
3. Was the search period or search date reported? Please specify.	Yes	AHRQ report is an Update of Nelson 2010 [164] November 1, 2009, through October 1, 2016, with active surveillance through March 23, 2018
4. Were at least the most important free-text terms or subject headings of the search strategy reported?	Yes	The search strategy for Pubmed is presented
Assessment (Questions 1.-4. All questions answered with "yes" = comprehensive information retrieval; one or more questions answered with no = questionable quality) a)	Yes	Comprehensive, with minor shortcomings in the implementation of the search strategy
a) If information sources listed in the project plan were not considered in the SRs/HTAs or were not searched comprehensively (e.g. study registries), these sources could be searched within the framework of information retrieval for the assessment.		

Description of the Evidence used

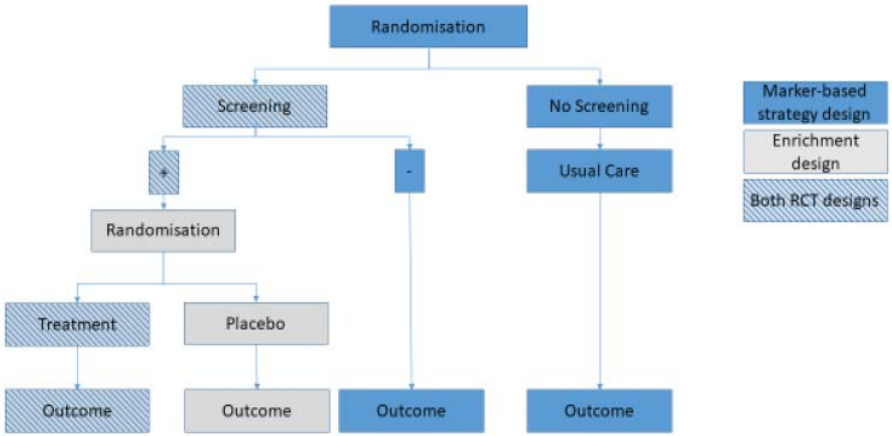

Figure 8: Graphical representation of study elements in marker-based strategy and enrichment design RCTs

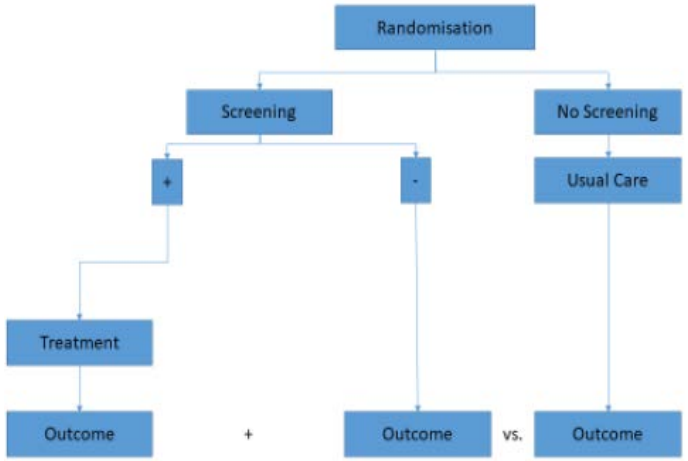

Figure 9: Graphical representation of study elements in marker-based strategy design RCTs

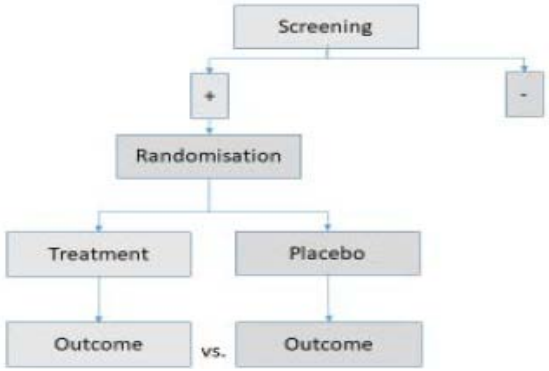

Figure 10: Graphical representation of study elements in enrichment design RCTs

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: Marker-based strategy design: In- and exclusion Criteria

Study	Major inclusion criteria	Major exclusion criteria
Core study pool: RCTs with marker-based strategy design		
SCOOP [16]	• Women, 70-85 years of age	• on prescription anti-osteoporosis drugs (excluding vitamin D or calcium) at the time of inclusion in the study • deemed unsuitable (e.g. by their GP[a]) to enter a research study (e.g., known dementia, terminally ill, or recently bereaved)
ROSE [17]	• Women, 65-80 years of age	• None mentioned
COSHIBA [18]	• Women, 65-80 years of age	• None

a: some primary care physicians did not invite women they thought were unsuitable (e.g. due to serious illness or cognitive impairment)
Abbreviations: e.g.: for example; GP: general practitioner; RCT: randomised controlled trial

Table A-3: Enrichment design: In- and exclusion Criteria

Study	Major inclusion criteria	Major exclusion criteria
Additional Evidence: RCTs with enrichment design		
FIT **Clinical Fracture study** [19]	• Female, 55-81 years of age • Postmenopausal for at least 2 years • Femoral neck BMD of 0.68 g/cm^2 [a] or less • No vertebral fracture	• recent peptic ulcers that required hospitalisation • dyspepsia requiring daily treatment • significant renal or hepatic dysfunction • medical problems that precluded 3 years of participation • severe malabsorption • blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic • myocardial infarction within 6 months • unstable angina • hypothyroidism • hyperthyroidism • hyperparathyroidism • oestrogen or calcitonin within preceding 6 months • bisphosphonates at any time • sodium fluoride (> 1 mg/d) at any time
FIT **Vertebral Deformity study** [20]	• Female, 55-81 years of age • Postmenopausal for at least 2 years • Femoral neck BMD of 0.68 g/cm^2 [a] or less • ≥ 1 vertebral fracture at baseline	

Study	Major inclusion criteria	Major exclusion criteria
Liang 2017 [21]	• Female, 50-65 years of age • Postmenopausal • Newly diagnosed osteoporosis • High risk of fracture • Lumbar vertebra BMD of T-Score – 2.5 to – 3.3 SD[b]	• Disease that severely affects the metabolism of bone or calcium • (e.g. diabetes, Cushing`s Syndrome, changes in function of the thyroid or parathyroid, osteomalacia, rheumatoid arthritis, multiple myeloma, bone tumour, osteoarthrosis, Paget`s disease, and osteogenesis imperfecta) • Severe primary cardiac diseases • Disease of the vessels or hematopoietic system • Sever liver function or renal insufficiencies • Taking drugs within the past 6 months that affect bone metabolism (e.g. oestrogen, steroid hormones, calcitonin, parathyroid hormones, bisphosphonates, fluoride, Vitamin D, anticonvulsant drugs, and diuretics • Medical history of mental illness • Alzheimer`s disease
Reid 2018 [23]	• Female, ≥ 65 years of age • Postmenopausal • Ambulatory • T-Score at either the total hip or the femoral neck on either side: -1.0 to -2.5 SD[b,c]	• Spinal osteoporosis only if T-Score was ≤ -3.0 SD • Estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^3 of body surface area • Major systemic disease • Cancer in the previous 2 years • Metabolic bone disease • Regular use of bone-active drugs in the previous year (including bisphosphonates, oestrogen, antioestrogens, and prednisolone at a dose of 2.5 mg or greater per day or equivalent)

Study	Major inclusion criteria	Major exclusion criteria
Yang 2015 [22]	• Female • Postmenopausal • T-Score at lumbar spine (L1-L4) or hip: ≤ - 2.5 SD[b]	• Smoking • Any secondary osteoporosis • Disease affecting bone metabolism (such as tumour, hypothalamic or pituitary disorders, diabetes mellitus or other chronic illnesses) • Prior history of fragility fractures • Previous or current use of glucocorticoids, oestrogens, bisphosphonates, fluorides, or calcium and vitamin D supplementation

a: This corresponds to 1,6 SD or more below the normal young adult white women but was believed to correspond to a BMD value of at least 2 SDs below the mean of normal young adult mean

b: Measured with DXA

c: a T-Score of less than -2.5 at 1 hip site (total hip or femoral neck on either side) did not preclude participation, as long as another hip site met the criteria

Abbreviations: BMD: bone density measurement; DXA: dual x-ray absorptiometry; e.g.: for example; L: lumbar vertebra; mg/d: milligrams per day; mm Hg: millimetre of mercury; SD: standard deviation

Table A-4: Characterisation of the population – Marker-based strategy design

Study	Country / Period of trial execution	Follow-up	Number (N)[a]	Age [years] mean (SD)	Sex [m/f] %	Dropouts n (%)	Ethnic group (%)	BMI (SD)	Previous fracture (%)	Fallen in past year
Marker-based strategy design										
SCOOP [16]	UK / 2008 - 2014	5 years	**I:** 6,233 **C:** 6,250	**I:** 75.4 (4) **C:** 75.5 (4)	0/100	**I:** 899 (14)[b] **C:** 923 (15)[b]	**I:** White: 6,157 (99) Black: 26 (< 1) Asian: 25 (< 1) Other: 15 (< 1) **C:** White: 6,160 (99) Black: 26 (< 1) Asian: 18 (< 1) Other: 23 (< 1)	**I:** 26.7 (5) **C:** 26.7 (5)	**I:** 1,399 (22)[c] **C:** 1,463 (23)[c]	**I:** 1,744 (28) **C:** 1,700 (27)
ROSE [17]	Denmark / 2010 - 2016	5 years	**I:** 17,072 **C:** 17,157	**I:** 71 [68;76][d] **C:** 71 [68;76][d]	0/100	**I:** 0 (0)[e] **C:** 0 (0)[e]	Not assessed	Not assessed	**I:** 981 (11)[f] **C:** 919 (10)[f]	Not assessed
COSHIBA [18]	UK / 2007 - 2010	1 year	**I:** 1,062 **C:** 2,138	**I:** 72.7 (4.3) **C:** 72.6 (4.3)	0/100	**I**: 103 (9.7)[b] **C**: 218 (10.2)[b]	Not assessed	Not assessed	**I:** 280 (26.4)[c] **C:** 558 (26.1)[c]	Not assessed

Study	Country / Period of trial execution	Follow-up	Number (N)[a]	Age [years] mean (SD)	Sex [m/f] %	Dropouts n (%)	Ethnic group (%)	BMI (SD)	Previous fracture (%)	Fallen in past year
a: number of randomised individuals b: Rapid REA authors` own calculation c: broken bone since age 50 years d: median [Q1; Q3] e: since data on outcomes were extracted from the NPR and the Danish Civil Registration Register, it was assumed that data from all randomised participants were available f: refers to women who were included with questionnaire data (Intervention: N=9,279; Control: N=9,326) **Abbreviations:** BMI: body mass index (kg/m2); C: Control group; f: female; I: Intervention group; m: male; N: number of randomised individuals; NPR: National Patient Registry); REA: relative effectiveness assessment; SD: standard deviation; UK: United Kingdom										

Table A-5: Characterisation of the population – Enrichment design

Study	Country / Period of trial execution	Follow-up	Number (N)	Age [years] mean (SD)	Sex [m/f] %	Dropouts n (%)	Ethnic group (%)	BMI (SD)	Previous fracture (%)	Fallen in past year
Enrichment design										
FIT Clinical Fracture study [19]	USA / 1992 - 1997	4 years	**I:** 2,214 **C:** 2,218	**I:** 67.6 (6) **C:** 67.7 (6)	0 / 100	171[a]	White (97) Other (3[a])	**I:** 24.9 (3.9) **C:** 25.0 (4.0)	**I:** 797[a] (36)[b] **C:** 776[a] (35)[b]	Not assessed
FIT Vertebral Deformity study [20]	USA / 1992 - 1996	3 years	**I:** 1,022 **C:** 1,005	**I:** 70.7 (5.6) **C:** 71.0 (5.6)	0 / 100	78[a]	Caucasian (97 %) Asian (1 %) African-American (1 %)	**I:** 25.5 (4.2) **C:** 25.6 (4.2)	**I:** 573[a] (57)[b] **C:** 583[a] (58)[b]	Not assessed
Liang 2017 [21]	China / 2010 - 2014	2 years	**I:** 175 **C:** 110	**I:** 57.2 (2.8) **C:** 57.5 (3.2)	0 / 100	**I:** 20 (11.4)[a] **C:** 15 (13.6)[a]	Not assessed	**I:** 22.7 (1.9) **C:** 23.1 (2.2)	Not assessed	Not assessed
Reid 2018 [23]	New Zealand / 2009 - 2018	6 years	**I:** 1,000 **C:** 1,000	**I:** 71 (5.0) **C:** 71 (5.1)	0 / 100	**I:** 963[a] (96) **C:** 966[a] (97)	European (94.5[a]) Other (5.5[a])	**I:** 26.8 (4.6) **C:** 26.9 (4.7)	**I:** 237 (23.7)[c] **C:** 238 (23.8)[c]	Not assessed
Yang 2015 [22]	China / No information	1 year	**I:** 50 **C:** 50	**I:** 61.4 (9.5) **C:** 59.7 (8.9)	0 / 100	**I:** 3 (6)[a] **C:** 2 (4)[a]	Not assessed	**I:** 22.1 (2.7) **C:** 22.8 (2.9)	Not assessed	Not assessed

a: Rapid REA authors` own calculation
b: history of fractures since age 45
c: history of non-vertebral fracture after 45 years of age
Abbreviations: BMI: Body Mass Index (kg / m2); C: control group; f: female; m: male; I: intervention group: N: number of randomised individuals; REA: relative effectiveness assessment; SD: standard deviation; UK: United Kingdom; USA: United States of America

Table A-6: Characterisation of the intervention – Marker-based strategy design

Study	Intervention	Control	Concomitant therapy
Marker-based strategy design			
SCOOP [16]	Recruitment Identification through primary care lists Exclusion of those, who were on prescription of anti-osteoporosis drugs were deemed unsuitable to enter a research study by their GP		
	Questionnaire Self-completed questionnaire[a] to capture the FRAX risk factors on osteoporosis-related fractures	Questionnaire Self-completed questionnaire[a] to capture the FRAX risk factors on osteoporosis-related fractures[b]	
	Randomisation		
	N = 6,233 **Screening** Calculation of the 10-year probability of hip and major osteoporotic fractures If the individual 10-year probability of hip fracture was below the threshold[c] probability for their age: letter (also copied to their GP) with a recommendation that no further action was necessary Bone mineral density measurement >>> if the individual 10-year probability of hip fracture was above the threshold[c] probability for their age: Invitation to assess BMD measurement (local, femoral neck BMD, DXA-based) Recalculation of individual 10-year hip fracture probability with inclusion of BMD Comparison of recalculated hip fracture probability with an assessment threshold for each 5-year age group. Communication of final risk category to participants and their GPs by letter	N = 6,250 Standard care	

Study	Intervention	Control	Concomitant therapy
	Treatment Participants above the threshold[c] were advised to make an appointment with their family doctor to discuss treatment options and received standard care as usual. Participants classified below the threshold[c] received a letter (also copied to their GP) confirming their low-risk status with a recommendation that no further action was necessary. Treatment not specified.		None mentioned
ROSE [17]	Recruitment Identification at random from the background population using the Danish Civil Registration system		
	Randomisation		
	N = 17,072 Questionnaire Self-administered questionnaires[d] comprising questions about fracture risk to enable calculation of FRAX **Screening** Calculation of individual 10-year fracture risk[e] (major osteoporotic fractures) Bone mineral density measurement >>> if the individual 10-year probability of major osteoporotic fractures was ≥ 15 %, women were offered a DXA-Scan[f]. **Treatment** The woman and her GP were informed of the result by letter[g]. Treatment not specified.	N = 17,157 Questionnaire Self-administered questionnaires comprising questions about fracture risk to enable calculation of FRAX – women were not informed about the result of the FRAX calculation **Treatment** Standard care as usual	None mentioned

Study	Intervention	Control	Concomitant therapy
COSHIBA [18]	Recruitment Recruited from multiple general practices (from a range of neighbourhoods and deprivation scores). GPs invited participants. Those who were deemed unsuitable by their GPs were not invited.		
	N = 1,062 Baseline data collection by self-completed questionnaires[h] prior to randomisation	N = 2,138 Baseline data collection by self-completed questionnaires[h] prior to randomisation	
	Randomisation		
	Healthy bone leaflet Provision of information on appropriate management of vertebral fractures **Screening** 20-minute appointment: data were collected on height loss, history of previous non-vertebral fractures, Margolis back pain score, and rib-to-pelvis-distance >>> if calculated risk score was below 4: identification as being “high risk” >>> offer of a thoracolumbar radiograph The report was sent back to the GP for further action **Treatment** Not specified	Healthy bone leaflet Provision of information on appropriate management of vertebral fractures **Treatment** Not specified	None mentioned

a: age, sex, height and weight and dichotomised risk variables including previous fragility fracture since the age of 50 years, parental history of hip fracture, current tobacco smoking, any long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and daily alcohol consumption of three or more units per day. If the respondent did not know the answer to an individual question, a negative response was assumed.

b: The risk of fracture will not be calculated from the questionnaire for subjects in the control arm

c: The 10-year probability of hip fracture for each participant was compared with an assessment threshold for each 5-year age group, as established previously in an analysis of treatment cost effectiveness in the UK [165]

d: 25 items on anthropometry, history of osteoporosis and fractures, menopause, risk factors for fractures, conditions associated with secondary osteoporosis, self-rated health and perceived risk of fractures.

e: The 10- year fracture probability was calculated for women returning the questionnaire with no more than three missing items on the FRAX variables

Study	Intervention	Control	Concomitant therapy
f: BMD of the lumbar spine (L1–L4) and total right hip (including neck, trochanter, and intertrochanter region) was measured with osteodensitometry using DXA (Hologic Discovery, Hologic Delphi, or Lunar Prodigy) and expressed in T-scores (SD differing from mean for young adults). Scanners were calibrated using spine phantom as suggested by the ISCD [166]. Standard procedure was followed at each site. g: Information for the GPs included treatment recommendations based on the Danish national guidelines, but the final decision for treatment was left to the patient and GP h: Age, parental hip fracture, smoking and alcohol use, use of glucocorticoids, previous fractures and secondary cause of osteoporosis, fall frequency, mobility and use of walking aid **Abbreviations:** DXA: Dual-energy x-ray absorptiometry; FRAX: Fracture Risk Assessment Tool; UK: United Kingdom; L: lumbar spine; ISCD: International Society for Clinical Densitometry; GP: general practitioner; SD: standard deviation; BMD: bone mineral density; N: number of patients evaluated			

Table A-7: Characterisation of the intervention – Enrichment design

Study	Intervention	Control	Concomitant therapy
Enrichment design			
Clinical Fracture study (FIT) [19] and **Vertebral Deformity study** (FIT) [20]	Recruitment Recruitment by mass mailings		

	Screening
	If responded by telephone: invited to a first screening visit
	First screening visit: check of preliminary inclusion criteria; if fulfilled: invited to BMD screening (hip, DXA)[a]
	If BMD ≤ 0.68 g/cm[b,c] : invitation to second screening visit
	Second screening visit: a vertebral radiograph was taken
	>>> if vertebral fractures were present: women were assigned to the Vertebral Deformity sub-study
	>>> if no vertebral fractures were present: women were assigned to the Clinical Fracture sub-study
	Randomisation of women to alendronate sodium or placebo in each sub-study		

	Randomisation		
	N = 2,214 **Treatment** First 2 years: 5 mg/d alendronate sodium[d] From third year: 10 mg/d alendronate sodium[d]	N = 2,218 **Treatment** Placebo[d]	If dietary calcium intakes was 1,000 mg/d or less, participants were asked to take a daily supplement containing 500 mg of elemental calcium and 250 IU of cholecalciferol (vitamin D)[e]

Study	Intervention	Control	Concomitant therapy
Liang 2017 [21]	Recruitment No information on recruitment process available.		
	Screening 800 women in the Zhejiang area were screened, of which 600 women were interested and were eligible for further screening[f] BMD (DXA[g]) and blood test[h] were performed >>> if T-Score was between -2.5 and -3.3 SD women were randomised to zoledronic acid or placebo		
	Randomisation		
	N = 175 **Treatment** 5 mg/year zoledronic acid[i,j]	N = 110 **Treatment** Placebo	None mentioned

Study	Intervention	Control	Concomitant therapy
Reid 2018 [23]	Recruitment Recruited with the use of electoral registers from the Auckland region of New Zealand (invitations for trial participations were mailed)		
	Screening BMD (either at the total hip or the femoral neck on either side)[k] No information available about the concrete procedure of the screening appointments.		
	Randomisation		
	N = 1,000 **Treatment** 5 mg every 18 months zoledronic acid[i]	N = 1,000 **Treatment** Placebo	Women who were not already taking vitamin D supplements were given a single oral dose of cholecalciferol (2.5 mg [100,000 IU]) at least 1 week before their first infusion and subsequently received cholecalciferol at a dose of 1.25 mg per month for the duration of the trial. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not supplied.

Study	Intervention	Control	Concomitant therapy
Yang 2015 [22]	Recruitment Recruited from the community through advertisements No information available about the concrete procedure of the screening appointments.		
	Screening BMD (dual x-ray absorptiometry at the lumbar spine [L1-L4] or total hip)[l]		
	Randomisation		
	N = 50 **Treatment** 5 mg/year zoledronic acid[i]	N = 50 **Treatment** Placebo	daily supplementation of 1,000 mg of calcium and vitamin D

a: QDR-2000, Hologic Inc., Waltham, Mass; The publication did not provide any information on any form of quality assurance, precision or calibration of the instrument.

b: The 10-year probability of hip fracture for each participant was compared with an assessment threshold for each 5-year age group, as established previously in an analysis of treatment cost-effectiveness in the UK

c: At the time of enrolment, this BMD Score was believed to correspond to a BMD value of 2 SD below the mean of normal young adult white women, based on the manufacturer`s reference values. Due to an update of the reference database for the derivation of the T-score after completion of the recruitment, this T-score had shifted to ≤ -1.6

d: participants should take the study drug with at least 120 ml of water in a fasting state and not lie down or eat or drink any other food or liquid for at least 30 minutes

e: supplements should be taken after breakfast

f: no information is available on how women were contacted

g: The publication did not provide any information on any form of quality assurance, precision or calibration of the instrument

h: routine chemical and blood turnover markers

i: intravenous

j: Bone mineral density of the lumbar spine (L1-4), both proximal femora and total body using a GE Prodigy dual-energy x-ray absorptiometer [23,167]

k: administered as a 15-min to 30-min intravenous infusion at baseline and at 12 month-visit

l: QDR-4500 (Hologic Inc., Waltham, MA, USA)

Abbreviations: DXA: dual energy x-ray absorptiometry; FRAX: fracture risk assessment Tool; GP: general practitioner; mg: milligrams; N: number of persons randomised; UK: United Kingdom; SD: standard deviation

List of planned, ongoing, withdrawn studies or completed studies without reported results

Table A-8 shows all studies identified by the information retrieval without previously reported results. Since the status of both studies was considered unclear, author inquiries were made (see also Table A-).

Table A-8: List of studies without reported results

Study Identifier	Country	Status/ Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
POROS [27]	Western USA	Unclear / 2012[a]	RCT (MB-SD)	1,836	Self-administered questionnaire[b] Stratification into 2 groups, based on the presence or absence of fracture risk factors: "No risk factors" or "≥ 1 risk factor" "≥ 1 risk factor"-individuals were randomised into intervention or control; "No risk factors"-individuals received usual care		Women aged 50 to 65 years, without previous prescription of osteoporosis medication. Women were excluded who: used an oestrogen implant, hormone therapy, or birth control pills within the past 6 months; had a terminal illness; lived in a long-term care facility; were enrolled in another clinical research study; or were a resident of the EU	Incident patient-reported fractures will be assessed if sample size is adequate (secondary outcome); Association between incidence of fractures and number and type of fracture risk factors will be determined
					Intervention: Urine NTx test[c] NTx < 50: DXA NTx ≤ 50: no DXA[d] Usual care[e]	Control: Usual care[e]		

Study Identifier	Country	Status/ Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
SALT [26][5]	Netherlands	Ongoing / not estimable[f]	RCT (MB-SD)	3,400	Self-administered questionnaire[g] If ≥ 1 clinical risk factor: randomisation		Women aged 65 to 90 years, who are not prescribed bone sparing drugs or corticosteroids and with at least one clinical risk factor for fractures, as determined by questionnaires	Primary outcome: Time to new fracture and number of fractures after 36 months in patients with high fracture risk according to FRAX assessment. Secondary outcomes: Time to new fracture; Number of fractures after 36 months; Death rate; Falls
					BMD[g] assessed with DXA[i] and IVA[j], fall risk assessment, and clinical chemistry screening According to treatment thresholds precise treatment instructions are given to the GP	Usual care[k]		
SLCTR/2018/038 [28]	Sri Lanka	Ongoing (11 / 2019)	RCT (ED)	60	Recruitment through electoral registers Fracture risk assessment: FRAX algorithm using clinical risk factors and bone mineral density values		Postmenopausal women with newly diagnosed osteoporosis and a high fracture risk High fracture risk: major fracture risk > 10 % and / or hip fracture risk > 3 %	Adverse events: Tolerability measured by the rate of "dropouts" due to the adverse effects of alendronate Adverse effects of medications - upper GI tract symptoms (i.e. abdominal pain, nausea, vomiting)
					oral alendronate (70 mg / week) with oral vitamin D3 (800 IU / day) for 6 months	placebo prepared similar to the alendronate tablet along with vitamin D3 (800 IU / day) for 6 months		

[5] The results of this study were published after our update search in May 2019 and could therefore not be included in this Rapid REA. Future assessments should take the results into account.

Study Identifier	Country	Status/ Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
a: estimated completion year: enrolment starting in August 2006 and ending in February 2008 with a planned follow-up of 24 months b: included questions about general health and fracture risk c: urine test for laboratory analysis of urinary NTx and creatinine; The samples were batched and run every 2 to 4 weeks. The results were reported in nM BCE/mM Cr. The urine NTx cut-off level chosen was 1 or more SD above the premenopausal mean (35 nM BCE/mM Cr±15). d: hip and lumbar spine e: no prescribed intervention as part of the study f: originally planned end of study: 2016-01-01 g: inspired by FRAX but without questioning long-term untreated hyperthyroidism, alcohol use and smoking h: non-dominant hip and spine (L1 to L4) i: Hologic Discovery device (Hologic Inc., USA) j: lateral image of the spine k: patients that have an indication for DXA and IVA according to Dutch guideline for GPs at the time of their inclusion, are notified accordingly and advised to contact their GP as part of usual care **Abbreviations:** BMD: bone density measurement; DXA: dual-energy x-ray absorptiometry; ED: enrichment design; EU: European Union; FRAX: Fracture Risk Assessment Tool; GP: general practitioner ; IVA: instant vertebral assessment; L: lumbar spine; MB-SD: marker-based strategy design; nM BCE/mM Cr: nanomole bone collagen equivalents per millimole creatinine; NTx: N-telopeptide; RCT: randomised controlled trial; SD: standard deviation; USA: United States of America								

Risk of bias tables

Table A-9: Risk of bias – Study level (RCTs)

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – study level
			Participant	Treating person			
Core study pool – RCTs with marker-based strategy design							
SCOOP [16]	Yes	Yes	No	No	Yes	Yes	Low
ROSE [17]	Yes	Yes[a]	No	No	Yes	Yes	Low
COSHIBA [18]	Yes	Unclear[b]	No	Yes	Yes	Yes	High[c]
Additional evidence – RCTs with enrichment design							
Vertebral Deformity study [20]	Yes	Unclear[b]	Yes	Yes	Yes	Yes	High[c]
Clinical Fracture study [19]	Yes	Unclear[b]	Yes	Yes	Yes	Yes	High[c]
Liang 2017 [21]	Unclear[b]	Unclear[b]	Yes	Yes	Yes	Yes	High[d]
Reid 2018 [23]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Yang 2015 [22]	Unclear[b]	Unclear[b]	Yes	Unclear[e]	Yes	Yes	High[f]

a: The publication does not contain any specific information on allocation concealment. However, no selection bias is assumed, since confounding variables should not have been present: the data of the participants were taken from registration registers and randomisation took place before recruitment.

b: Due to missing information

c: Due to unclear allocation concealment

d: Due to unclear generation of randomisation sequence, unclear allocation concealment and unclear selective outcome reporting

e: The study is described as double-blind, but it remains unclear who was blinded in addition to the patient

f: Due to unclear generation of randomisation sequence, unclear allocation concealment and unclear blinding of the treating person

Abbreviations: RCT: randomised controlled trial

Table A-10: Risk of bias – Symptomatic fractures

Fractures	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
SCOOP [16]	Low	Yes	Yes	Yes	Yes	Low
ROSE [17]	Low	Unclear[a]	Yes	Yes	Yes	Low
COSHIBA [18]	High	Yes	Yes	Yes	Yes	High[b]
Additional evidence – RCTs with enrichment design						
Vertebral Deformity study [20]	High	Yes	Yes	Yes	Yes	High[b]
Clinical Fracture study [19]	High	Yes	Yes	Yes	Yes	High[b]
Liang 2017 [21]	High	Yes	No	Unclear[d]	Yes	High
Reid 2018 [23]	Low	Yes	Yes	Yes	Yes	Low
Yang 2015 [22]	High	Unclear[c]	Yes	Unclear[d]	Yes	High[e]

a: Unclear due to missing information
b: Due to high risk of bias on study level
c: The study is described as double-blind, but it remains unclear who was blinded in addition to the patient
d: No study registry entry could be identified
e: Due to high risk of bias on study level and unclear blinding of outcome assessors
Abbreviations: ITT: intention to treat; RCT: randomised controlled trial

Table A-11: Risk of bias – Back pain

Back pain	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
---	---	---	---	---	---	---
Additional evidence – RCTs with enrichment design						
Vertebral Deformity study [20]	High	No	Unclear[a]	Unclear[a]	Yes	High
Clinical Fracture study [19]	High	No	Unclear[a]	Unclear[a]	Yes	High

a: unclear due to missing information
---: the outcome was not reported
Abbreviations: ITT: intention to treat; RCT: randomised controlled trial

Table A-12: Risk of bias – (Serious) adverse events

(Serious) adverse events	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
---	---	---	---	---	---	---
Additional evidence – RCTs with enrichment design						
Vertebral Deformity study [20]	High	Yes	Yes	Yes	Yes	High[a]
Clinical Fracture study [19]	High	Yes	Yes	Yes	Yes	High[a]
Liang 2017 [21]	High	Yes	No	Yes	Yes	High[b]
Reid 2018 [23]	Low	Yes	Yes	Yes	Yes	Low

a: Due to high risk of bias on study level

b: Due to high risk of bias on study level and inadequately realized ITT principle. Additionally, adverse events are only reported, if they occurred in more than 5 % of participants and within 3 days after drug admission

c: The study is described as double-blind, but it remains unclear who was blinded in addition to the patient

---: the outcome was not reported

Abbreviations: ITT: intention to treat; RCT: randomised controlled trial

Table A-13: Risk of bias – Mortality

Mortality	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
SCOOP [16]	Low	No	Yes	Yes	Yes	Low
Additional evidence – RCTs with enrichment design						
Vertebral Deformity study [20]	High	Yes	Yes	Yes	Yes	High[a]
Clinical Fracture study [19]	High	Yes	Yes	Yes	Yes	High[a]
Reid 2018 [23]	Low	Yes	Yes	Yes	Yes	Low
Yang 2015 [22]	High	Unclear[c]	Yes	Yes	Yes	High[a]

a: due to high risk of bias on study level

b: due to missing information

c: The study is described as double-blind, but it remains unclear who was blinded in addition to the patient

---: the outcome was not reported

Abbreviations: ITT: intention to treat; RCT: randomised controlled trial

Table A-14: Risk of bias – Utilisation of healthcare resources

Utilisation of healthcare resources	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
---	---	---	---	---	---	---
Additional evidence – RCTs with enrichment design						
Vertebral Deformity study [20]	High	Unclear[a]	Yes	Yes	Yes	High[b]

a: The data were actively requested, but it is unclear whether the allocation was known to the outcome assessors or not.

b: due to high risk of bias on study level. Additionally it was unclear, whether outcome assessors were blinded and whether the ITT principle was adequately reported.

---: the outcome was not reported

Abbreviations: ITT: intention to treat; n.a.: not assessable; RCT: randomised controlled trial

Table A-15: Risk of bias – Health-related quality of life

Health-related quality of life	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Core study pool – RCTs with marker-based strategy design						
SCOOP [16]	Low	No	Yes	Yes	Yes	High[a]
Additional evidence – RCTs with enrichment design						
---	**---**	**---**	**---**	**---**	**---**	**---**

a: due to unblinded outcome assessor, participants and treating persons

---: the outcome was not reported

Abbreviations: ITT: intention to treat; RCT: randomised controlled trial

Table A-16: GRADE assessment – Clinical fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Clinical fractures												
2 MB-SD	Low[a]	Not serious	Not serious	Not serious	None	7,295	8,388	HR: 0.94, [0.86; 1.03] [16] OR: 0.6, [0.35; 1.03] [18]	Clinical fractures in 5 years: 160 per 1000[b]	151 per 1000 [139; 165]	High ++++	
5 ED	High[c]	Not serious	Very serious[d]	Not serious	unknown operationalisation of the outcome in 2 out of 5 trials	4,441	4,368	HR: 0.81, [0.71; 0.92] [19,20][e] HR: 0.73, [0.60; 0.90] [23] No fractures occurred in Yang 2015 and Liang 2017			Very low +OOO	

a: low risk of bias in over 70 % of the weight of relevant studies

b: assumption of baseline risk for clinical fractures after 5 years taken from SCOOP: 0.16

c: due to high risk of bias on study level in 3 out of 4 studies, likely outcome reporting in 1 study, unclear blinding of the outcome assessor in 1 study, and unclear selective outcome reporting in 2 out of 4 studies

d: downgraded by 2 levels for enrichment design

e: pooled HR from meta-analysis (Rapid REA authors` own calculation)

Abbreviations: C-Group: control group; CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; OR: odds ratio; REA: relative effectiveness assessment

Table A-17: GRADE assessment – Osteoporosis-related fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Osteoporosis-related fractures												
2 MB-SD	Low	Not serious	Not serious	Not serious	none	23,305	23,407	HR: 0.99, [0.94; 1.04][a] [16,17]	Osteoporosis-related fractures in 5 years: 132 per 1000[b]	131 per 1000[b] [125; 137]	High ++++	
0 ED	---	---	---	---	---	---	---	---	---		---	

a: relative effect from meta-analysis (Rapid REA authors` own calculation)

b: absolute risks for major osteoporotic fractures after 5 years obtained by naïve pooling of results from SCOOP and ROSE

Abbreviations: CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; REA: relative effectiveness assessment

Table A-18: GRADE assessment – Hip fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Hip fractures												
3 MB-SD	Low[a]	Serious[b]	Not serious	Not serious	none	24,367	25,545	Hip fractures in 5 years: HR: 0.72, [0.59; 0.89] [16] SHR: 1.01, [0.89; 1.14] [17] OR: 1.01, [0.25; 4.71] [18]	Hip fractures in 5 years: 35 per 1000[c] 31 per 1000[e]	25 per 1000[d] [21; 32] 31 per 1000[f] [28; 35]	Moderate +++O	

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
3 ED	High[g]	Not serious	Very serious[h]	Not serious	none	4,236	4,223	HR 0.65, [0.41; 1.04][i] [19,20] HR: 0.66 [0.27; 1.16] [23]			Very low +OOO	

a: overall low risk of bias since 2 out of 3 RCTs are of low risk of bias
b: downgrade by 1 level for heterogeneous results and differences in study design
c: assumption of baseline risk for hip fractures after 5 years taken from SCOOP: 3.5 %
d: assumption of baseline risk for hip fractures after 5 years is calculated via HR
e: assumption of baseline risk for hip fractures after 5 years taken from ROSE: 3.1 %
f: assumption of baseline risk for hip fractures after 5 years is calculated via SHR
g: due to high risk of bias on study level in 2 out of 3 studies
h: downgraded by 2 levels for enrichment design
i: relative effect from meta-analysis (Rapid REA authors` own calculation)
Abbreviations: CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; REA: relative effectiveness assessment; SHR: sub hazard ratio

Table A-19: GRADE assessment – Major osteoporotic fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Major osteoporotic fractures												
1 MB-SD	Low	NA (only 1 trial)	Not serious	Not serious	none	17,072	17,157	SHR 0.99, [0.92; 1.06] [17]	Not estimable		High ++++	
0 ED	---	---	---	---	---	---	---	---			---	
Abbreviations: CI: confidence interval; ED: enrichment design; MB-SD: marker-based strategy design; NA: not applicable; SHR: sub hazard ratio												

Table A-20: GRADE assessment – Clinical vertebral fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Importance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Clinical vertebral fractures												
1 MB-SD	High[a]	NA (only 1 trial)	Not serious	Serious[b]	none	1,062	2,138	OR **0.33**, [0.04; 2.79] [18]	Not estimable		Low ++OO	
3 ED	High[c]	Not serious	Very serious[d]	Not serious	none	4,236	4,223	RR: 0.53, [0.36; 0.77][e] [19,20] HR: 0.41 [0.22; 0.75] [23]			Very low +OOO	

a: due to high risk of bias on study level (unclear allocation concealment)
b: downgraded by 1 level due to a large CI
c: due to high risk of bias on study level in 2 out of 3 studies
d: downgraded by 2 levels due to enrichment design
e: relative effect from meta-analysis (Rapid REA authors` own calculation)
Abbreviations: CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; NA: not applicable; OR: odds ratio; REA: relative effectiveness assessment; RR: relative risk

Table A-21: GRADE assessment – Other clinical fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Other clinical fractures												
1 MB-SD	High	NA (only 1 trial)	Not serious	Serious[a]	none	1,062	2,138	OR **0.65**, [0.33; 1.28] [18]	Not estimable		Low ++OO	
2 ED	High	NA (only 1 trial)	Very serious[b]	Not serious	none	3,236	3,223	HR 0.85, [0.73; 1.00][c] [19,20]			Very low +OOO	

a: downgraded by 1 level due to results were only available from 1 study conducted with this screening approach (i.e. lack of replication)

b: downgraded by 1 level due to enrichment design

c: relative effect from meta-analysis (Rapid REA authors` own calculation)

Abbreviations: CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; NA: not applicable; OR: odds ratio; REA: relative effectiveness assessment

Table A-22: GRADE assessment – Wrist fractures

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Symptomatic fractures												critical
Wrist fractures												
1 MB-SD	High[a]	NA (only 1 trial)	Not serious	Serious[b]	none	1,062	2,138	OR **0.41**, [0.17; 1.00] [18]	Not estimable		Low ++OO	
3 ED	High[c]	Serious	Very serious[d]	Not serious	none	4,236	4,223	OR: 1.19, [0.87; 1.64] [19] OR: 0.52, [0.31; 0.87] [20] HR: 0.56 [0.37; 0.85] [23]			Very low +OOO	

a: due to high risk of bias on study level (unclear allocation concealment)
b: downgraded by 1 level due to results were only available from 1 study conducted with this screening approach (i.e. lack of replication)
c: due to high risk of bias on study level in 2 out of 3 studies
d: downgraded by 2 levels due to enrichment design
Abbreviations: CI: confidence interval; ED: enrichment design; HR: hazard ratio; MB-SD: marker-based strategy design; NA: not applicable; OR: odds ratio

Table A-23: GRADE assessment – Back pain

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Back pain												
0 MB-SD **1 ED**	--- High	--- Not serious	--- Very serious[a]	--- Not Serious	--- none	--- 1,022	--- 1,005	--- ≥ 7 bed rest day(s) due to back pain RR: 0.44, [0.30; 0.64] [31]	--- Not estimable		--- Very low +OOO	important
								New or worsened disability due to back pain RR: 0.85, [0.63; 1.15] [31]	Not estimable			
								Back pain OR: 1.06 [0.52; 2.17] [21]	Not estimable			

a: downgraded by 2 levels due to enrichment design
b: downgraded by 1 level due to results are available from 1 study only (i.e. lack of replication)
Abbreviations: CI: confidence interval; ED: enrichment design; MB-SD: marker-based strategy design; OR: odds ratio; RR: relative risk

Table A-24: GRADE assessment – Utilisation of healthcare resources

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Utilisation of healthcare resources												
0 MB-SD 1 ED	--- High	--- NA (1 trial only)	--- Very serious[a]	--- Serious[b]	--- none	--- 1,022	--- 1,005	--- Utilisation of any healthcare resource OR: 0.73, [0.54; 0.98] [31]	--- Not estimable		--- Very low +OOO	important
								Utilisation of emergency room OR: 0.70, [0.52; 0.96] [31]	Not estimable			
								Utilisation of hospital OR: 0.73, [0.47; 1.13] [31]	Not estimable			
								Utilisation of nursing home / rehab OR: 0.65, [0.33; 1.29] [31]	Not estimable			

a: downgraded by 2 levels due to enrichment design

b: downgraded by 1 level due to results are available from 1 study only (i.e. lack of replication)

Abbreviations: CI: confidence interval; ED: enrichment design; MB-SD: marker-based strategy design; NA: not applicable; OR: odds ratio

Table A-25: GRADE assessment – (Serious) adverse events

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
(Serious) adverse events												
0 MB-SD	---	---	---	---	---	---	---	---	---		---	important
Alendronate												
2 ED	High[a]	Not serious	Very serious[b]	Not serious		3236	3223	Any gastric or duodenal perforations, ulcers, and bleeding RR: 0.86, [0.59; 1.24][c] [33]	Not estimable		Very low +OOO	
								Discontinuation of study medication due to upper GI tract symptoms RR: 1.15, [0.87; 1.54][c] [33]	Not estimable			
								Serious atrial fibrillation RR: 1.51, [0.97; 2.40] [34]	Not estimable			

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
								Serious oesophageal events RR: 2.19, [0.80; 6.95][c] [33]	Not estimable			
Zoledronic acid												
1 ED	Low	NA (1 study only)	Very serious[b]	Not serious	none	1,000	1,000	Serious adverse events OR: 0.84, [0.70; 1.00] [23]	Not estimable		Low ++OO	
								Composite of vascular events[d] OR: 0.76, [0.52; 1.09] [23]	Not estimable			
								Cancer[e] OR: 0.67, [0.50; 0.89] [23]	Not estimable			
								Atrial fibrillation OR: 0.98, [0.67; 1.44] [23]	Not estimable			

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
1 ED	High	NA (1 study only)	Very serious[b]	Not serious	large effects, but outcome only reported within 3 days after drug admission and only if occurred in ≥ 5 % of patients[f]	155	95	Headache (influenza-like illness) OR: 0.729, [1.67; 31.38] [21]	Not estimable		Very low +OOO	
								Pyrexia OR: 11.77, [3.45; 39.19] [21]	Not estimable			
								Myalgia OR: 6.39, [2.19; 18.66] [21]	Not estimable			
								Arthralgia OR: 1.79, [0.85; 3.74] [21]	Not estimable			
								No studies were found that looked at screening strategies using other drugs than alendronate or zoledronic acid.				

a: due to high risk of bias on study level (unclear allocation concealment)
b: downgraded by 2 level due to enrichment design
c: pooled data from both the Clinical Fracture study and Vertebral Deformity study
d: sudden death, myocardial infarction, coronary-artery revascularisation, or stroke
e: excluded non-melanoma skin cancers
f: evaluation valid for Liang 2017
Abbreviations: CI: confidence interval; ED: enrichment design; GI: gastro-intestinal; MB-SD: marker-based strategy design; OR: odds ratio; RR: relative risk

Table A-26: GRADE assessment – Mortality

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considerations	Number of patients		Relative effect (95% CI)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Mortality												
1 MB-SD	Low	NA (only 1 trial)	Not serious	Not serious	none	6,233	6,250	HR: 1.05, [0.93; 1.19] [16]	Mortality in 5 years: 84 per 1000[a]	Mortality in 5 years: 88 per 1000[b] [78 to 99]	High ++++	important
4 ED	High	Not serious	Very serious[c]	Not serious	none	4,286	4,273	HR 0.92, [0.59; 1.45] [19] OR: 1.13, [0.62; 2.04] [20] OR: 0.65, [0.40; 1.05] [23] No deaths in Yang 2015 [22]			Very low +OOO	

a: assumption of baseline risk for hip fractures after 5 years taken from SCOOP: 8.4 % (C-Group)

b: assumption of baseline risk for hip fractures after 5 years taken from SCOOP: 8.8 % (I-Group)

c: downgraded by 2 levels due to enrichment design

Abbreviations: C-Group: control group; CI: confidence interval; ED: enrichment design; HR: hazard ratio; I-Group: intervention group; MB-SD: marker-based strategy design; no.: number; OR: odds ratio; SD: standard deviation

Table A-27: GRADE assessment – Health-related quality of life

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Mean (SD)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
Health-related quality of life												
1 MB-SD	High	NA (only 1 trial)	Not serious	Not serious	none	6,233	6,250	EQ-5D Mean Score I-Group:0.63 (0.33) Mean Score C-Group: 0.63 (0.32) difference: p = 0.154 [16]	Not estimable		Moderate +++O	important
								SF-12 (physical health) Mean Score I-Group:38.3 (16.7) Mean Score C-Group: 38.3 (16.6) difference: p = 0.237 [16]	Not estimable			

Number and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other consider ations	Number of patients		Mean (SD)	Anticipated absolute effects [95% CI]		Quality	Impor-tance
						Screening	No Screening		Risk without screening	Risk with screening		
0 ED	---	---	---	---	---	---	---	SF-12 (mental health) Mean Score I-Group: 46.0 (18.3) Mean Score C-Group: 46.3 (18.2) difference: p = 0.554 [16] ---	Not estimable ---		---	

Abbreviations: CI: confidence interval; ED: enrichment design; MB-SD: marker-based strategy design; SD: standard deviation

Applicability tables

The following table focuses only on the two large strategy design studies SCOOP and ROSE, as COSHIBA and studies with enrichment design provided only limited information.

Table A-28: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Only postmenopausal women were investigated in the included studies. Therefore, the findings only apply to this subpopulation. No statement can be made about men or pre- or perimenopausal women.
Intervention	The intervention in the included studies contained various screening strategies. In the main “conventional” screening-studies of this Rapid REA a combination of FRAX, subsequent DXA and anti-osteoporosis treatment was investigated. FRAX scores are country specific and it is unknown how much the various models differ and whether the risk profile (and therefore possibly the treatment response) of the patients will differ due to those adaptations or not. Additionally, the treatment was at the discretion of the GPs, it was not specified in the studies and only drug treatment was described in 1 of the publications of the included screening studies. Despite these uncertainties, the results of the included studies seem in principle transferable to the European context.
Comparators	The control was no screening or usual care in all studies with marker-based strategy design. In 1 study, the control group was informed about a bone-healthy lifestyle, which can be considered a sufficiently similar control intervention. Overall, the requirements of the control group appear to be transferable to all European countries where “grey”[a] screening is carried out and a certain availability of DXA is given. ROSE showed that about 25 % of the control group received a DXA examination (compared to the intervention arm: 48 %). In Denmark, screening in the general population is currently not reimbursed according to the survey presented in table A1 in appendix 2. The example shows, however, that the proportion of screening examinations carried out is not negligible.
Outcomes	In the 2 large RCTs with marker-based strategy design (SCOOP and ROSE), fracture rates were assessed over a period of 5 years. Therefore, no issue regarding applicability was identified. However, applicability of the results in terms of outcomes is clearly limited by the lack of interpretable data on (serious) adverse events.
Setting	All studies with marker-based strategy design were conducted in Western Europe; Most of the screening was carried out in a multi-centre setting, while the treatment was then initiated and carried out by GPs. This could well correspond to a typical procedure. Since in all strategy design trials the women of the control group were each asked to fill in a questionnaire on fracture risk factors, it can be assumed that more women in the control group became aware of the risk of osteoporosis and went to their GP to be tested for osteoporosis rather than would be expected in a screening naïve population. Therefore, the setting can only be transferred to the real world context to a limited extent.

a: This refers to a screening performed on the initiative of the patient on the basis of identified risk factors.
Abbreviations: BMD: bone mineral density measurement; GP: general practitioner; RCT: randomised controlled trial

Questionnaire on the disease and its treatment

Participation in a benefit assessment of IQWiG (English translation)

Questionnaire describing a disease and its treatment for people affected or patient organisations

General information

The Institute for Quality and Efficiency in Health Care (IQWiG) produces independent, evidence-based reports for example on drugs, non-drug interventions (e.g. surgical procedures) or on diagnostic tests and screening tests. Based on the IQWiG report the Federal Joint Committee (G-BA), as the supreme decision-making body of self-government in health care, decides whether a medical service is to be reimbursed by the statutory health insurance funds.

IQWiG also works in a European network of comparable institutions. The European Union funds this network (EUnetHTA). The aim is to jointly review new treatments so that the European Member States can decide on the basis of the common assessment whether the new treatment should be introduced and paid for in the relevant part of Europe.

For consideration of the perspective of people affected, IQWiG has developed this questionnaire for dissemination of information about the disease and its treatment. The feedback from people affected or patient organisations is included in the benefit assessment. For this purpose, a response soon after the start of the procedure is required.

Please support us with your knowledge of the disease and its treatment and fill out this questionnaire for the project

Screening for osteoporosis

from the perspective of people affected and send it by the

3rd August 2018

either by e-mail to eunethta@iqwig.de or by post (original documents) to the following address:

IQWiG

Department of Non-Drug Interventions

“EUnetHTA“

Im Mediapark 8

50670 Cologne

In addition, it is required to send a completed form for disclosure of potential conflicts of interests. The form was sent to you together with this questionnaire in the English original and the German translation.

If you submit the documents first by e-mail, send the originals (with your handwritten signature) no later than 10 working days after the deadline mentioned above, i.e. by **17th August 2018** to the above-mentioned address.

Please note that only information submitted in time can be taken into account for the benefit assessment. More detailed explanations and a list of frequently asked questions can be found at the end of this questionnaire.

1.1 Contact information

Please enter your contact information below and if necessary, name the patient organization in whose name you complete the questionnaire.

Name (for inquiries):

E-mail-address:

Phone:

Name of patient organisation:

Function within patient organisation:

Website:

1.2 Declaration of consent

To publish the information you provided in the context of the benefit assessment, we require the following declaration of consent. Please allow us to use your information by providing the necessary signature.

Declaration of consent: I am aware that, if applicable, the name of the patient organisation and all the information in Sections 2 to 4 of this questionnaire can be published online in the EUnetHTA report on the benefit assessment.

Place and date:

Signature:

1.3 Declaration of potential conflicts of interest

Please complete the form for disclosure of potential conflicts of interest and submit it together with the replied questionnaire. For support, you will find a German translation of the original sheet attached. Please sign on the original English sheet.

Explanations to the form can be found at

https://www.iqwig.de/en/participation/conflicts-of-interest/frequently-asked-questions-about-the-form-for-disclosure-of-potential-conflicts-of-interest.3307.html.

2 Information about the disease

2.1 Experience of patients and people affected with the disease

What are the impairments and aspects associated with the disease for this area of application in everyday life and, among other things, affect quality of life?

To help you with the answer we have formulated some questions as suggestions. It is not necessary to answer every single question!

Possible aspects for answering the questions may be:

(1) Which aspects and symptoms of the disease are more important to treat or to control than others?

(2) How does the illness affect your daily life (job, family, leisure time) or the life of the affected person?

(3) What influence does the illness have on your occupational situation or that of patients?

(4) Are there activities that you or people affected are unable to do due to their illness?

(5) If the disease persists for an extended period. Is there anything that is important to consider in the course of the disease?

(6) What are the challenges for the care of people with this condition?

(7) What impact does the treatment have on the daily routine of care?

Here you can enter the answers to Question 2.1

2.2 Need to consider special patient groups

Is it important to consider special patient groups?

To help you with the answer we have formulated some questions as suggestions. It is not necessary to answer every single question!

Some examples for different patient groups:

(1) Are there important differences between men and women?

(2) Are there important differences regarding younger and older patients?

(3) Are there important differences regarding disease phases?

(4) Are there differences in ethnic groups?

Here you can enter the answers to Question 2.2

3 Information on the treatment of the disease

3.1 Experience of those affected with the currently available therapies for the area of application

How well can you manage the disease with the therapies you know?

To help you with the answer we have formulated some questions as suggestions. It is not necessary to answer every single question!

Possible aspects that could be relevant for this question:

(1) What therapies are you or people affected currently using to treat the disease in the area of application?

(2) How effective is the current therapy in the treatment of the disease?

(3) How are different areas of life (job, family) affected by therapy?

(4) Are there any side effects that are more difficult or better tolerated than others?

(5) Is there anything important in the course of treating the disease?

(6) Based on the experience of some or several people affected, is there a need that is not covered by the current therapy? What is the need? Is this true for all or only for a specific group of people affected (e.g. men/ women)?

Here you can enter the answers to Question 3.1

3.2 Expectations for a new therapy

What expectations do you or the people affected have of a new therapy? You can consider both drug therapies and non-drug therapies.

To help you with the answer we have formulated some questions as suggestions. It is not necessary to answer every single question!

Examples of possible aspects:

(1) What problems (such as side effects) are known to you that might occur with current therapies and that should be addressed in a new therapy?

(2) Is there a specific gap in current therapy that should be addressed by the new therapy?

(3) Which side effects are acceptable and which are not?

(4) What expectations do you have regarding the application of the new therapy?

(5) Are there any expectations of the dosage form of a new therapy?

Here you can enter the answers to Question 3.2

4 Additional information

Do you have any further information that you would like to share with IQWiG (voluntary information)?

Here you can enter the answers to Question 4

5 Questions and answers

In the following, you will find questions and answers regarding the consideration of the perspective of the people affected in IQWiG's benefit assessments within the context of EUnetHTA.

5.1 How much time do the people affected or patient organisations have to complete the questionnaire?

To answer the questionnaire, the people affected and patient organisations have 15 working days at their disposal. The exact submission date is noted in the questionnaire. Decisive for timely submission is the date of receipt at the institute. In order to meet the deadline timely receipt by e-mail is initially sufficient. The original documents (i.e. questionnaire and completed forms for disclosure of potential conflicts of interest) must be submitted within 10 working days. Alternatively, the original documents can also be submitted directly before the deadline; then a submission by e-mail is not required. The submitter is responsible for the timely receipt of the completed questionnaire before the deadline and for the timely receipt of the original documents no later than 10 working days after the deadline.

5.2 What other requirements must be met?

In order to take into account the information you provide it is also required that the form for disclosure of potential conflicts of interest is fully completed and submitted in time.

Explanations on the form can be found at:

https://www.iqwig.de/en/participation/conflicts-of-interest/frequently-asked-questions-about-the-form-for-disclosure-of-potential-conflicts-of-interest.3307.html

The relationships you have disclosed in the form can be published in the benefit assessment.

It is only stated whether or not there are conflicts of interest in the area covered by the question, i.e. only the answer "yes" or "no" is provided. No specific details on business relationships or the amount of any remuneration received will be published.

5.3 Where should the completed documents be sent?

You can send documents by e-mail to the following address: eunethta@iqwig.de. Original documents should be sent to the following address: IQWiG, Department of Non-Drug Interventions, keyword “EUnetHTA“, Im Mediapark 8, 50670 Cologne

5.4 Should quoted literature be attached to the questionnaire?

If you cite literature, it will be helpful if you also provide it to us by e-mail. However, this is not mandatory.

5.5 Do you have any further questions regarding the procedure or contents of the questionnaire?

If you have questions about the procedure or contents of the questionnaire, you can contact eunethta@iqwig.de.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A-29: Survey results (verbatim responses)

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Austria	**HVB**	General population screening for osteoporosis is currently not offered.	NA	NA	NA	NA	
Austria	**GÖG**	see answer HVB					
Croatia	**Former AAZ (now MoH)**	General population screening nor other screening for osteoporosis currently are not offered in Croatia nor planned in the near future.	NA	NA	NA	NA	
Denmark	**DEFACTUM**	General population screening for osteoporosis is currently not offered in Denmark. There are a few hospitals, which offer a Fracture Liaison Service (FLS), including people with fractures, but not a screening of people in general.	NA	NA	NA	NA	

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Germany	**IQWiG**	Screening for osteoporosis is not reimbursed in the general population. Osteodensitometry is reimbursed in order to optimize the therapy decision if, on the basis of concrete anamnestic and clinical findings, for example in clinically manifest vertebral or hip fracture without adequate trauma, there is an intention for a specific drug treatment of osteoporosis. For the purpose of optimizing the therapy decision, osteodensitometry can be repeated at the earliest after 5 years, unless earlier osteodensitometry is required due to special therapy-relevant anamnestic and clinical findings.	NA	NA	NA	NA	
Hungary	**OGYEI**	There is no organised screening for osteoporosis in the general population in Hungary. Only opportunistic screening on a case by case basis.	NA	NA	NA	NA	

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Ireland	**HIQA**	General population screening for osteoporosis is not offered in Ireland. Targeted high risk assessments for osteoporosis are offered	Men and women with: Previous low trauma fracture; X-ray evidence of osteopenia; Corticosteroid use (i.e. prednisolone for three months or more); Family history of osteoporosis (especially maternal hip fracture); Other clinical risk factors: height loss, kyphosis, low Body Mass Index (<19 kg/m2); Possible secondary osteoporosis: primary hyperparathyroidism, poorly controlled thyrotoxicosis, malabsorption, rheumatoid arthritis, liver disease, alcoholism, primary hypogonadism. Women with: Untreated oestrogen deficiency (surgical or natural menopause <45 years, secondary amenorrhoea > 6 months not due to pregnancy or primary hypogonadism)	Not an organised programme, so there may be variations in care particularly given the public / private mix. The 2008 report by the National Screening Group advocates use of DXA scan	No	N/A	https://www.hse.ie/eng/services/publications/olderpeople/strategy-to-prevent-falls-and-fractures-in-irelands-ageing-population---full-report.pdf

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Italy	**RER**	Screening for osteoporosis is not recommended	NA	NA	NA	NA	
Italy	**de Veleto**	General population screening for osteoporosis is currently not offered in Italy.		NA	NA	NA	NA
Lithuania	**VASPVT**	General population screening for osteoporosis is currently not offered.	NA	NA	NA	NA	
Norway	**NIPH**	General population screening for osteoporosis is currently not offered in Norway. In case of risk factors or fractures, diagnostic studies may be conducted. Osteoporosis screening of healthy women is offered by private/commercial health care, and sometimes also by physicians in public health care, but we do not know how frequent this is.	NA	NA	NA	NA	
Poland	**AOTMiT**	Currently the European Social Fund grant is used to launch Polish national osteoporosis screening program. Programs of this kind need to be positively assessed by the AOTMiT before launching. The program is under organisation; when it starts will be active till 2023. Additionally to screening activities an education for patients and physicians will be offered.	Women 50-70 y.o.	FRAX + densytometry + X-ray	Yes	FRAX + densytometry + X-ray	

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Romania		General population screening for osteoporosis is currently not offered in Romania. There is a national program for the treatment of osteoporosis covered by social health insurance. Passive screening is used in order to identify patients for this program. Patients are included in the program based on specific thresholds of T (SD) DXA score, fracture/bone fragility and FRAX. All the tests are covered by health insurance. Screening for general population is offered by private companies or research centers	NA	NA	NA	NA	http://www.cnas.ro/page/programul-national-de-boli-endocrine.html http://www.tevapharm.ro/Media/News/Pages/2014/campanie-screening-osteoporoza%E2%80%93masuratori-qus.aspx http://www.cdt-babes.ro/articole/osteoporoza-rezultate-program-prevenire.php

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Slovenia	**JAZMP and MoH Slovenia**	General population screening for osteoporosis is currently not reimbursed in the general population. DXA is reimbursed just in case of secondary osteoporosis. The fracture risk assessment program financed from the public fund (supported by FRAX program) is provided in the references ambulatory care (on the primary health care level) by the graduated nurses for the patients with the high fracture risk.	In fracture risk assessment program are included patients at high fracture risk.	The fracture risk assessments is supported by FRAX program	The fracture risk assessment programforin is organised in references ambulatory care (on the primary health care level)	FRAX	https://www.dlib.si/stream/URN:NBN:SI:DOC-0ZKCLJIC/f18948a8-5cc2-4749-aa18-56b6b16ec944/PDF
Spain	**AETS-ISCIII**	General population sistematic and organized screening for osteoporosis is currently not offered. Densitometry (DXA) is recommended by clinical guidelines and can be offered from primary care on the basis of individual clinical risk (fracture risk).	NA	NA	NA	NA	

Country	HTA agency	What is the reimbursement status for screening for osteoporosis in your country?*	If screening is being reimbursed by social health care/offered by public health service				Link
			Who is eligible for screening (e.g. general population, patients with risk factors, age groups)*	What is /are the testing algorithm(s) used in your country (e.g. FRAX, DXA, qUS… or combinations of them)*	Is the screening organised in a programme?*	What testing algorithm is used in the programme? (e.g. FRAX, DXA, qUS… or combinations of them)*	
Spain	**AQUAS**	There is a 2014 Consensus Document published by the MoH recommending to perform opportunistic screening in primary care addressed to people aged 70 or more. Additionally, it is recommended in the same document, to perform an active detection in people of the same age involved in specific already existing programs (e.g. "attention to chronic patients programs or for elderly"). This is not directly related specifically with the concept "osteoporosis", but on frailty and risk of falling	People aged 70 or more (see the C column for more details)	FRAX is an option to be considered at the following MoH funded report (goo.gl/GopHjt) although the level of implementation is unknown and it is not part of the main consensus document presented at column C	No	NA	
UK	**NICE**	General population screening for osteoporosis is currently not offered. This recommendation is currently under review	NA	NA	NA	NA	https://legacyscreening.phe.org.uk/osteoporosis
UK/Scotland	**SHTG**	General population screening for osteoporosis is currently not offered.	NA	NA	NA		

* Please report in separate lines if screenings offered vary for different populations.

Abbreviations: DXA: dual-energy x-ray absorptiometry; FRAX: fracture risk assessment tool; NA: not applicable; qUS: quantitative ultrasound; SD: standard deviation

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1.	**Ethical**	
1.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2.	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2.	**Organisational**	
2.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	Screening for osteoporosis in the general population requires easy access to the technology. In addition, it should be ensured that sufficient equipment (DXA-devices) is available for screening purposes as well as for treatment monitoring.	
2.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3.	**Social**	
3.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4.	**Legal**	
4.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
	The use of ionising radiation may affect legal aspects.	
4.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

APPENDIX 4: MISCELLANEOUS

Table A-30: Documentation of queries to study authors in the assessment report

Study	Content of query	Reply received yes / no	Content of reply
Completed studies			
SCOOP study [16]	▪ Single event rates for the number of patients with ▫ Fractures of the shoulder/humerus (ICD10:S42) ▫ Fractures of the forearm (ICD10: S52) ▫ Fractures of the femur (ICD10: S72. Except S72.0, S72.1 and S72.2) ▫ Fractures of the lower leg (ICD10: S82) ▫ Fractures of the spine, that were symptomatic (S12.0, S12.1, S12.2, S12.19, S22, S32, T08) ▫ Any other fractures	no	--
ROSE study [17]	▪ Single event rates for the number of patients with ▫ Fractures of the shoulder/humerus (ICD10:S42) ▫ Fractures of the forearm (ICD10: S52) ▫ Fractures of the femur (ICD10: S72. Except S72.0, S72.1 and S72.2) ▫ Fractures of the lower leg (ICD10: S82) ▫ Fractures of the spine, that were symptomatic (S12.0, S12.1, S12.2, S12.19, S22, S32, T08) ▫ Any other fractures ▪ How many deaths occurred in each of the 2 study arms?	no	--
Studies without published results			
POROS study [27]	▪ What is the status of the study? Publication of results on patient-relevant outcomes available? If not, when can it be expected?	no	--
SALT study [26][6]	▪ What is the status of the study? When can a publication of results be expected?	no	--

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts, as well as responses from the author, is available on the EUnetHTA website.

[6] The results of this study were published after our update search in May 2019.