EUnetHTA Joint Action 3 2016-2020

Screening for osteoporosis in the general population

Project ID: ***OTCA19***

Project description and planning

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)

Swiss Network for HTA (SNHTA)

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Version Log

Version number	Date	Modification	Reason for the modification
V1	08/11/2018	Specification of the sections “inclusion criteria” and “project scope” according to population, intervention and comparison due to different RCT designs Addition of a table of the main osteoporosis drug treatments currently used in Europe	Inclusion of details on enrichment design studies (new creation of table 2-5, update of table 2-7)
		Time frame for systematic reviews added (focused search, Tab 2-3)	Input from dedicated reviewers
		“Usual care“ deleted, as this operationalization is already included in the term “no screening“; this also results in changes in the PICO table (2-7)	
		Editorial modifications	
V2	03/12/2018	Clarification of the meaning of the terms "osteoporotic fractures" and "fragility fractures"	Input from external experts
	13/12/2018	Updating of the schedule “milestones and deliverables”	Adjustment after extension of the scope (inclusion of studies with enrichment design) and to the effort of the collaboration in the project

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List of abbreviations

AHRQ	Agency for Healthcare Research and Quality
AQuAS	Agency for Health Quality and Assessment of Catalonia
CE	Conformité Européenne (European Conformity)
CUR	health problem and current use of technology
DXA	dual-energy x-ray absorptiometry
EFF	effectiveness
EUnetHTA	European network for Health Technology Assessment
e.V.	eingetragener Verein, registered association
FRAX	Fracture Risk Assessment Tool
GÖG	Gesundheit Österreich GmbH
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HTA	health technology assessment
I	inclusion criterion
IQWiG	Insitut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Insitute for Quality and Efficiency in Health Care
LBI-HTA	Ludwig-Boltzmann-Institute for Health Technology Assessment
NICE	National Institute for Health and Care Excellence
NSPHMPD	National School of Public Health, Management and Professional Development
RCT	randomised controlled trial
REA	Relative Effectiveness Assessment
SAF	safety
SNHTA	Swiss Network for HTA
SR	systematic review
TEC	description and technical characteristics of technology
PICO	population, intervention, comparison, outcome
PTH	parathyroid hormone
qCT	quantitative computed tomography
qUS	quantitative ultrasonography
U.S.	United States
WHO	World Health Organisation
WPs	work packages

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Author	Germany	• Develop the first draft of the project plan • Perform the literature search and study selection • Undertake the assessment (data extraction, analysis, synthesis, interpretation of findings, answer assessment elements) • Prepare the draft rapid assessment • Circulate drafts project plan, rapid assessment) to dedicated reviewers and external experts, compile and respond to feedback, and edit draft report, as appropriate • Prepare final assessment and write a final summary of the assessment
2.	Swiss Network for HTA (SNHTA)	Co-author	Switzerland	• Collaboration in the development of the project plan • Check, provide input and endorse all steps (in particular: collaboration in literature selection [perform the literature screening as the second screener], data extraction, assessment of risk of bias) • Develop the first draft of the domains “Description and technical characteristics of the technology (TEC)” and “health problem and current use of technology (CUR)” in the Rapid Relative Effectiveness Assessment (REA) • Check, provide input and endorse content of all domains • Collaborate in the writing of the discussion and conclusions, and endorse these sections • Review drafts of the assessment, propose amendments where necessary and provide written feedback
3.	Agency for Health Quality and Assessment of Catalonia (AQuAS)	Dedicated reviewer	Spain	• Review the first draft project plan and the first draft rapid assessment, propose amendments where necessary and provide written feedback • Review methods, results and conclusions based on the original studies included • Provide constructive comments in all project phases
4.	Gesundheit Österreich GmbH (GÖG)	Dedicated reviewer	Austria	
5.	National School of Public Health, Management and Professional Development (NSPHMPD)	Dedicated reviewer	Romania	

Contributors				
6.	Johannes Flechtenmacher specialist in orthopaedics and trauma surgery (osteology), rehabilitation, physical therapy, chiropractice	External clinical expert	Germany	• Ensure clinical correctness by thoroughly reviewing the preliminary PICO, the second draft project plan and the second draft rapid assessment concerning clinical aspects • Review methods, results, and conclusions based on the original studies included • Provide constructive comments in all project phases • Answer specific questions of the assessment team about the disease, the intervention, the comparator and outcomes, which may arise during the scoping and assessment phases
7.	Alexander Mann specialist in internal medicine, endocrinology and diabetology	External clinical expert		
8.	Rafael Azagra Ledesma specialist in family and community medicine and clinical pharmacology	External clinical expert	Spain	
9.	Marta Zwart Salmerón specialist in family and community medicine	External clinical expert		
10.	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	Medical editor	Germany	• Medical and technical editing
11.	Ludwig-Boltzmann-Institute for Health Technology Assessment (LBI-HTA)	Project manager	Austria	• Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
Bundesselbsthilfeverband für Osteoporose e.V. - patient organisation (answers of 3 patients received on time)	By filling in a questionnaire on the disease and its treatment, the input of patients helps to clarify and provide patient-relevant outcomes.
Netzwerk Osteoporose e.V. - patient organisation (no answers received)	

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**July 23th, 2018**	**September 2019**
Scoping phase	**July 2018**	**December 2018**
Identification of external experts and patients	July 23th, 2018	September 2018
Ask patients to fill in a questionnaire describing the disease and its treatment	July13th, 2018	August 3rd, 2018
Scoping and development of draft Project Plan incl. preliminary PICO	July 23th, 2018	September 28th, 2018
Share the preliminary PICO with external experts for comments	October 10th, 2018	October 17th, 2018
Internal scoping e-meeting with the assessment team	August 29th, 2018	
Consultation of draft Project Plan with dedicated reviewers	October 23th, 2018	October 29th, 2018
Consultation of draft Project Plan with external experts	November 8th, 2018	November 22th, 2018
Amendment of draft Project Plan & final Project Plan available	November 23th, 2018	December 19th, 2018
Assessment phase	**November 2018**	**June 2019**
Writing of the first draft rapid assessment	November 22th, 2018	May 30th, 2019
Review by dedicated reviewer(s)	May 31th, 2019	June 14th, 2019
Writing of the second draft rapid assessment	June 17th, 2019	July 08th, 2019
Review by external clinical experts	July 09th, 2019	July 29th, 2019
Writing of the third draft rapid assessment	July 30th, 2019	August 25th, 2019
Medical editing	August 26th, 2019	September 6th, 2019
Writing of the fourth version of rapid assessment, Formatting	September 7th, 2019	September 13th, 2019
Final version of rapid assessment	Week from September 16th – September 20th, 2019	

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to jointly produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those jointly produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (Rapid) Relative Effectiveness Assessment.
2.	To apply this jointly produced assessment to a local (e.g. regional or national) context.	Production of ≥ 2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research question as to whether screening for osteoporosis in the general population using clinical risk assessment tools (e.g. Fracture Risk Assessment Tool, [FRAX]) and/or densitometry (e.g. dual-energy x-ray absorptiometry [DXA], quantitative computed tomography [qCT]/quantitative ultrasonography [qUS] of bone) followed by pharmacological and/or non-pharmacological measures to prevent osteoporotic fractures is more effective and/or safer than no screening in the general population. The relevance of the topic arises from the fact that osteoporosis is an increasingly relevant health problem. In addition, new evidence from randomised controlled trials (RCTs) has recently been published.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The aim of this systematic review is to examine the benefits and harms (clinical effectiveness and safety aspects) of a screening programme for osteoporosis in the general population with regard to patient-relevant outcomes. It seems likely that in some studies the terms "osteoporotic fractures" and "fragility fractures" are used synonymously. Therefore, the term "osteoporotic fractures" will include "fragility fractures" in this assessment. The selection of assessment elements will be based on the EUnetHTA Core Model for Rapid Relative Effectiveness Assessments (REA) (Version 4.2) [1]. The selected assessment elements with generic questions will be translated into research questions (please see Appendix 5.1). The checklist for potential ethical, organisational, patient and social and legal aspects of the HTA Core Model for Rapid REA will also be filled in (please see Appendix 5.2).

Description and technical characteristics of the technology (TEC) and the health problem and current use of technology (CUR) domains

The TEC and CUR domains will be 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 the TEC and CUR domains, no quality assessment tool will be used, but multiple sources will be used in order to validate individual, possibly biased sources. A descriptive analysis of different information sources will be performed.

Clinical effectiveness (EFF) and safety (SAF) domains

The example of the SCOOP-Trial [2] shows that the implementation of RCTs, as the study type with the highest level of evidence [3], is possible in this context. Therefore, only RCTs are to be included in this assessment that examine the entire screening process, including the subsequent pharmacological and/or non-pharmacological measures to prevent osteoporotic fractures. The most valid RCT design in this assessment will be the marker-based strategy design, as this is the only RCT design in which population groups, rather than patient groups, are randomly assigned to two full treatment strategies, including both the screening tests and all treatments. If the effects differ in the two treatment strategies, this difference can be attributed causally to the use of the marker [4].
Other RCT designs, such as the interaction and the enrichment design randomise participants only after screening. That is why they are unable to investigate the direct consequences of screening (including non-response to screening invitation).
Application of an interaction design would imply that all (mostly healthy) participants are randomised to either an anti-osteoporotic treatment or no treatment, which appears neither feasible nor ethical.
In an enrichment design, only positively tested participants are randomised to either an anti-osteoporotic treatment or no treatment. However, this design does not allow assessment of the consequences of a negative screening test (e.g. adverse effects in persons with a false-negative test result). Still, enrichment designs are useful for investigating treatment results of the positively tested individuals. Therefore, this form of evidence can support the evidence from marker-based strategy design studies. Here, however, it is essential that the study population of the enrichment design studies corresponds to the general population that would also be suitable for screening. The results of therapeutic RCTs on patients with symptomatic osteoporosis are clearly less transferable to a screening context. Therefore, enrichment designs will only be eligible for the present assessment if study participants clearly came from the general population and were newly identified by a positive screening test. Because drug therapy is currently the main component of anti-osteoporotic treatment, the inclusion of enrichment designs will be limited to RCTs comparing anti-osteoporotic drug treatment with placebo or no treatment.
A linked-evidence approach is possible [5], but is unlikely to produce sufficient certainty of results in this context. The collection of data on the test accuracy of the screening tests, which link them to efficacy data on anti-osteoporotic treatment, is a methodologically weak approach, as osteoporosis is a disease with different degrees of severity and different underlying aetiologies. It is therefore questionable whether the patients identified by a screening test (in a test accuracy study) are sufficiently similar to those receiving anti-osteoporotic treatment (in a drug study or other study). The linking of evidence thus leads to uncertainties, so that this approach is inappropriate.

To identify and classify patient-relevant outcomes, the following sources are considered: the European guidance for diagnosis and management of osteoporosis in postmenopausal women [6], the EUnetHTA guidelines on clinical endpoints and safety, and the information provided in the questionnaires by patients diagnosed with osteoporosis (and/or patient representatives) with regard to the disease and its treatment.

The validity of the studies and outcomes and the level of evidence will be assessed according to the EUnetHTA guidelines. The quality of the body of evidence will be assessed on the basis of GRADE (Grading of Recommendations, Assessment, Development and Evaluation, [7]). Relevant subgroup

analyses will in particular be assessed for the most important outcomes. The results of the patient-relevant outcomes reported in the studies are described comparatively in the report.

The results are checked for risk of bias for each outcome and for each study. The Cochrane risk of bias tool will be used on the study and outcome level. The results are described, merged and analysed. If possible, the procedures described in “Meta-analyses” and “Subgroup analyses and other effect modifiers” (see sections below) are used. A summarising evaluation of the information is performed.

Exclusion of study results

In general, results are not considered in the assessment if they are based on less than 70% of the randomised patients, i.e. if the proportion of patients not included in the evaluation is greater than 30% [8]. Exceptions to this rule are made, for example, if for logistical reasons no data were collected for entire centres and this was already provided for in the study planning [9]. The results are not considered in the assessment if the difference in the proportions of patients not included is greater than 15 percentage points between the groups.

Inconsistency of results (heterogeneity)

When carrying out a meta-analysis, the existence and the extent of potential heterogeneity are statistically examined. In the case of heterogeneity, the reasons must be investigated first. These can be methodological (see section “sensitivity analyses” below) and/or clinical (see section “subgroup characteristics and other effect modifiers” below). If unexplained heterogeneity is present, the quality of the evidence is 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 have to 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 guideline on direct and indirect comparisons: [https://www.eunethta.eu/wp-content/uploads/2018/03/Direct_comparators_comparisons.pdf).

The estimated effects and confidence intervals from the studies are summarized using forest plots. Subsequently, the study pool is examined for the presence of heterogeneity both visually and using the statistical tests [10]. If the heterogeneity test yields a statistically insignificant result ($p \geq 0.05$), it is assumed that estimating a common (pooled) effect usually makes sense, as long as no reasons (clinical/design) exist against applying this approach. In the case of at least 5 studies, meta-analysis is performed using the random effects model using the Knapp-Hartung method and the Paule-Mandel heterogeneity estimator [11]. As a result, the common effect including the confidence interval is displayed. Because heterogeneity cannot be reliably estimated when only a few studies are available, fixed effect models may be used in the event of 4 or fewer studies, as long as no other reasons against applying this approach exist; for instance, the studies must be sufficiently similar. If a model with a fixed effect is not justifiable, a qualitative summary can be provided.
If the heterogeneity test yields a statistically significant result ($p < 0.05$), only the prediction interval is shown if at least 5 studies are available. For 4 or fewer studies, a qualitative summary is provided.
Apart from the models mentioned above, alternatives such as the beta binomial model can be used for binary data [12] in certain situations and with special justification.

Subgroup analyses and other effect modifiers

The results are examined with regard to potential effect modifiers, i.e. clinical factors influencing the effects. The aim is to uncover possible 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. The results from regression analyses, which include interaction

terms, and the results from subgroup analyses will be included in the assessment. In addition, the project team conducts its own analyses in the form of meta-regressions or meta-analyses, categorising the studies with regard to possible effect modifiers. Subgroup analyses are only performed if each subgroup comprises at least 10 people and at least 10 events have occurred in one of the subgroups for binary data. It is intended to include the following potential effect modifiers:

- sex,
- age,
- body weight,
- ethnicity.

If further possible effect modifiers should arise from the available information, these can also be included, if reasonable (e.g. order of screening elements, DXA upfront versus FRAX followed by DXA). If potential effect modifiers are identified, the statements derived from the observed effects may be specified. For example, the benefit may be restricted to a specific subgroup of patients.

Sensitivity analyses

To evaluate the robustness of results, the assessment may include sensitivity analyses with regard to methodological factors. These factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

During the assessment, the sensitivity analyses presented in the Rapid REA and the corresponding methods applied will be evaluated.

Table 2-3: Planned literature search strategy

Literature search strategy
TEC and CUR domains The information retrieved for the TEC and CUR domains will be based on: • current clinical guidelines and systematic or narrative reviews, which will be 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 pharmacological and non-pharmacological treatment, and the best available epidemiological data. The clinical experts will be asked to verify the relevance and accuracy of the information and citations, • input from other HTA agencies on the current use of the technology. **EFF and SAF domains** A 2-step approach will be performed with the aim of producing results efficiently and using already existing scientific evidence at the highest level of evidence. 1) In a first step, systematic reviews (SRs) / health technology assessments (HTAs) are searched for in a focused search covering the period from 2013 onwards. If SRs / HTAs include RCTs fulfilling the inclusion criteria of the assessment report, the quality of information retrieval (including methods used for study selection) is checked in these documents. The aim is to find high-quality and up-to-date SRs / HTAs from which primary studies are identified. In this procedure, the primary studies identified in SRs / HTAs will be used for data extraction and assessment. 2) In a second step, an update search is conducted for primary studies published in the period not covered by the SRs / HTAs. 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 will be searched within the framework of information retrieval for the assessment.

Sources of information retrieval for systematic reviews (focused)

Bibliographic databases

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

Websites of HTA agencies

Additionally the websites of HTA agencies (NICE, AHRQ) will be searched for systematic reviews.

Sources of information retrieval for primary studies (comprehensive)

Bibliographic databases

- MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials

Study registries

- U.S. National Institutes of Health. Clinical Trials.gov
- World Health Organisation. International Clinical Trials Registry Platform Search Portal

Further sources of information and search techniques

- Queries to authors

In order to clarify essential issues for missing data, authors of publications of potentially relevant studies will be contacted by the main author of the assessment report (via e-mail, if e-mail address is available in the publication). Queries will only be sent out if the questions are likely to have a direct impact on the assessment's conclusion.

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, will be both reviewed and assessed with regard to their relevance by one person from the authoring team. A second reviewer from the co-authoring team will check 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 are 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 are screened against the inclusion and exclusion criteria

The selection of studies retrieved from the searches in bibliographic databases and study registries will be performed by two reviewers independently of each other (one from the authoring team and one from the co-authoring team). Discrepancies are resolved by discussion.

Data management

- Endnote X8 will be used for citation management
- Study selection will be performed in IQWiG's internal web-based trial selection database (webTSDB [13]).

Inclusion criteria

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

Table 2-4: 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 bone density measurement (DXA, qUS, qCT) followed by pharmacological (see section *Anti-osteoporosis drug treatment*) and/or non-pharmacological 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 [14] 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. CONSORT: Consolidated Standards of Reporting Trials; I: inclusion criterion; RCT: randomised controlled trial; qUS: quantitative ultrasonography, qCT: quantitative computed tomography	

Table 2-5: Inclusion criteria for enrichment design RCTs (supportive 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: pharmacological anti-osteoporosis treatment (as described in the section below "Anti-osteoporosis drug treatment")
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 [14] 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. CONSORT: Consolidated Standards of Reporting Trials; I: inclusion criterion; RCT: randomised controlled trial; qUS: quantitative ultrasonography, qCT: quantitative computed tomography	

Anti-osteoporosis drug treatment

According to the current European guidance [6], the following active substances are considered to be major pharmacological interventions:

1.) selective estrogen-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.) strontium ranelate
5.) denosumab

Procedures in the case 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 included patients 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 included patients will only be included if subgroup analyses are available for patients who meet the inclusion criteria [15].

Table 2-6: Plan for data extraction

Planned data extraction
All the information necessary for the assessment is extracted from the documents of the included studies and inserted into standardised tables. Data to be extracted from the studies include: • Information about the study (authors, year of publication, country, setting, study design, clinical trial identification number/ registry identifier and funding source, duration of the study) • Participant/patient characteristics (number of participants in the trial, age, sex, body weight, ethnicity) • Intervention and control characteristics (description of procedure, frequency of intervention per patient, potential accompanying disease/therapy (e.g. non-pharmacological anti-osteoporotic therapy), dosage) • Outcomes (outcomes examined (see section 2.2.2)), methods used to analyse outcome data, length of follow up, loss to follow up)

2.2.2 Project Scope

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/ **need to be consulted** throughout the assessment process.

Table 2-7: Project Scope: PICO

Description	**Project Scope**	
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.		
Population	**Marker-based strategy design**	**Enrichment design**
	Target population[1]: general population	Patients who were i) selected from the target population[1] ii) newly diagnosed with osteoporosis using a clinical risk assessment tool and/or bone density measurement (DXA, qUS, qCT)
Intervention	**Marker-based strategy design**	**Enrichment design**
	Screening for osteoporosis using • clinical risk assessment tools (e.g. FRAX) and/or • bone density measurement (DXA, qUS or qCT) followed by pharmacological (as described in the section "*Anti-osteoporosis drug treatment*", Table 2-5) and/or non-pharmacological measures to prevent osteoporotic fractures.	Pharmacological anti-osteoporosis treatment (as described in the section "*Anti-osteoporosis drug treatment*", Table 2-5)
Comparison	**Marker-based strategy design**	**Enrichment design**
	No screening Rationale: The rationale for "no screening" in the general population is chosen because this reflects the current situation in European countries: "At present, there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture. With the increasing	No treatment, placebo Rationale: The comparison with no treatment or placebo reflects the current situation in European countries. As screening for osteoporosis is not performed in the general population, people with asymptomatic and undiagnosed osteoporosis do not receive any anti-osteoporotic medication.

	development of effective agents and price reductions, this view may change, particularly for elderly people. In the absence of such policies, patients are identified opportunistically using a case finding strategy on the finding of a previous fragility fracture or the presence of significant risk factors." [6]	
Outcomes	Effectiveness- and safety-related: Critical outcome[2]: • symptomatic fractures Important outcomes[2]: • mortality (overall and fracture-related) • health-related quality of life • pain • body function and activities of daily living • use of resources (visits to doctors and hospitals, admission to nursing homes) • adverse events Rationale: We have chosen the outcomes based on the European guidance for diagnosis and management of osteoporosis in postmenopausal women [6], the EUnetHTA guidelines on clinical endpoints and safety, and the information provided in the questionnaires by patients diagnosed with osteoporosis with regard to patient-relevant outcomes. 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 which compare an anti-osteoporotic drug treatment with no drug treatment or placebo); no marker-by-treatment interaction designs	

[1] 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 [previous] osteoporotic fracture, organ transplant receivers, patients with cystic fibrosis, inflammatory bowel disease, etc.) will be excluded.

[2] Description of the importance of the outcomes according to GRADE [7]

DXA: dual-energy x-ray absorptiometry; FRAX: Fracture Risk Assessment Tool; RCT: randomised controlled trial; qCT: quantitative computed tomography; qUS: quantitative ultrasound

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	29/08/2018	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager
	To internally discuss and reach consensus on the first draft project plan.	26/09/2018	E-Meeting	Author(s), co-author(s)

3.1 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://eunethta.eu/rapid-reas/.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.2 Collaboration with stakeholders

Collaboration with manufacturer(s)

No manufacturers are included in the preparation of this Rapid REA. This is due to the fact that the technology under assessment is the entire screening process and therefore the focus is not on the evaluation of a single diagnostic or therapeutic product or technology.

Collaboration with other stakeholders

Patients with primary osteoporosis were identified through self-help groups and asked to complete a questionnaire on the disease and its treatment. The information provided is used to clarify and define patient-relevant outcomes.

3.3 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project in order to prepare activities to improve national uptake of the final assessment. The involved parties will be asked by WP6 [Quality Management] to provide feedback on the WP4 REA process and this information will be processed by WP6 to improve the quality of the process and output.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Author, co-author(s) and dedicated reviewers who declare a specific conflict of interest will be excluded from all of the work on this specific topic. However, they may still be included in other assessments.

Conflict of interest declarations are collected from external experts and patients involved. External experts or patients who declare a specific conflict of interest will be excluded from parts or all of the work on this specific topic. However, they still may be included in other assessments.

4 References

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5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	M	What is screening for osteoporosis? What procedure elements are included in the entire screening and treatment-process?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking? [This assessment element can be placed either in the TEC OR in the CUR domain]	Yes	M	For which indications have each of the potential technical devices and pharmaceuticals received marketing authorisation or CE-marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	M	What is the claimed benefit of screening for osteoporosis in relation to no screening in the general population?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of development and implementation of screening for osteoporosis in the general population?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers the different parts of the screening and treatment-process for osteoporosis? In what context is it provided? In what kind of care settings is it used (e.g. GP practices)?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	No	NM	---
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies are needed to screen for osteoporosis?
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]	*Yes*	*NM*	What is the reimbursement status of the technology?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What is osteoporosis?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	NM	What are the known risk factors for osteoporosis?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of osteoporosis?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	M	What are the symptoms and the burden of osteoporosis for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	No	NM	---
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How is osteoporosis currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	M	How is osteoporosis currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes - critical	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	M	How many people belong to the target population in the different European countries? Are there differences in the epidemiology?
A0011	Utilisation	How much are the technologies utilised?	Yes	M	How much is screening for osteoporosis practised in Europe to guide pharmacological management and fracture prophylaxis?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes - critical	M	What is the expected beneficial effect of screening for osteoporosis on mortality?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes - critical	M	How does screening affect symptoms and findings (severity, frequency) of osteoporosis?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	M	How does screening for osteoporosis in the general population affect progression of the disease or health condition?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	M	How does screening for osteoporosis affect body function?
D0016	Function	How does the use of technology affect	Yes	NM	How does the use of screening for osteoporosis in the general

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		activities of daily living?			population affect activities of daily living?
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes - critical	M	What is the effect of screening for osteoporosis on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes - critical	M	What is the effect of screening for osteoporosis on generic disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	No	NM	---
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	M	How safe is screening for osteoporosis in relation to no screening?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	NM	Are the harms related to dosage or frequency of applying the technology?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	M	How does the frequency or severity of harms change over time or in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	What are the susceptible patient groups that are more likely to be harmed by the procedure of the screening process?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	NM	---
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	No	NM	---

5.2 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.	
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?	No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No