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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

Scoping Report

Title	Denosumab (Prolia®) for the treatment of osteoporosis
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Technology	Denosumab (Prolia®)
Date	7 May 2021
Type of Technology	Pharmaceuticals

Conflicts of Interest

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Executive Summary

Osteoporosis is a bone disorder resulting in lower bone mineral density and an increased fracture risk. Denosumab (Prolia®) is used for the treatment of osteoporosis by reducing bone resorption. In recent years, evidence has indicated a rebound effect after denosumab discontinuation. Consequently, the Swiss Federal Office of Public Health is re-evaluating the available evidence for denosumab (Prolia®) in osteoporotic patients. The objective of the proposed Health Technology Assessment (HTA) is to compare the safety, effectiveness, cost-effectiveness, and legal, social, ethical and organisational impacts of denosumab compared to placebo, bisphosphonates and selective oestrogen receptor modulators in subgroups of patients with osteoporosis.

A systematic literature search was conducted in eight biomedical databases, in conjunction with clinical trial registries and speciality websites. From the 9,377 records obtained, 74 systematic reviews were identified, from which 21 randomised controlled trials (RCTs) were pearled and included. The search found 15 economic studies matching the inclusion criteria. Further, 4 studies reported social considerations, and 4 studies reported organisational considerations. The scoping searches did not identify any literature related to the ethical or legal implications of limiting denosumab (Prolia®).

There is sufficient RCT evidence to meta-analyse the safety and efficacy of denosumab (Prolia®) in post-menopausal women with osteoporosis and women with breast cancer on adjuvant aromatase inhibitors therapy; limited evidence exists for the remaining two sub-populations, therefore, evidence for these populations will be discussed narratively. For the HTA, the analysis will be stratified by population groups and subgroups. The design of the health economic evaluation will depend on the best available clinical evidence. The approach will include cost-effectiveness models and will produce an incremental cost-effectiveness ratio for each comparator. Additionally, a budget impact analysis will be conducted. There were limited social, ethical, legal and organisational studies identified from databases searches.

Zusammenfassung

Osteoporose ist eine Knochenerkrankung, die zu einer geringeren Knochenmineraldichte und einem erhöhten Frakturrisiko führt. Denosumab (Prolia®) wird zur Behandlung von Osteoporose eingesetzt, indem es die Knochenresorption reduziert. In den letzten Jahren gab es Hinweise auf einen Rebound-Effekt nach Absetzung von Denosumab. Daher wertet das Bundesamt für Gesundheit die verfügbare Evidenz für Denosumab (Prolia®) bei Patientinnen und Patienten mit Osteoporose neu aus. Das Ziel des vorgeschlagenen Health Technology Assessment (HTA) ist der Vergleich von Denosumab mit Placebo, Bisphosphonaten und selektiven Östrogenrezeptormodulatoren bezüglich Sicherheit, Wirksamkeit, Kosteneffektivität sowie rechtlicher, sozialer, ethischer und organisatorischer Auswirkungen in Untergruppen von Patientinnen und Patienten mit Osteoporose.

Es wurde eine systematische Literaturrecherche in acht biomedizinischen Datenbanken in Verbindung mit klinischen Studienregistern und spezialisierten Websites durchgeführt. Aus den 9377 erhaltenen Datensätzen wurden 74 systematische Reviews identifiziert, aus denen 21 randomisierte kontrollierte Studien (RCTs) herausgefiltert und eingeschlossen wurden. Die Suche ergab 15 ökonomische Studien, die den Einschlusskriterien entsprachen. Des Weiteren befassten sich 4 Studien mit sozialen und 4 Studien mit organisatorischen Überlegungen. Die Scoping-Recherchen ergaben keine Literatur zu den ethischen oder rechtlichen Auswirkungen der Einschränkung von Denosumab (Prolia®).

Es gibt ausreichend RCT-Evidenz für eine Meta-Analyse der Sicherheit und Wirksamkeit von Denosumab (Prolia®) bei postmenopausalen Frauen mit Osteoporose und bei Frauen mit Brustkrebs unter adjuvanter Aromatasehemmer-Therapie. Für die beiden übrigen Untergruppen gibt es nur begrenzte Evidenz, daher wird die Evidenz für diese Gruppen narrativ diskutiert. Für den HTA wird die Analyse nach Bevölkerungsgruppen und Untergruppen stratifiziert. Die Gestaltung der gesundheitsökonomischen Bewertung hängt von der besten verfügbaren klinischen Evidenz ab. Der Ansatz beinhaltet Kosten-Effektivitäts-Modelle, und es wird dabei ein inkrementelles Kosten-Effektivitäts-Verhältnis für jeden Komparator erstellt. Zusätzlich wird eine Budget-Impact-Analyse durchgeführt. Bei der Datenbankrecherche wurden nur wenige soziale, ethische, rechtliche und organisatorische Studien identifiziert.

Synthèse

L'ostéoporose est un trouble des os qui a pour effet de réduire leur densité minérale et d'augmenter le risque de fracture. Le denosumab (Prolia®) est utilisé pour traiter cette maladie en diminuant la résorption osseuse. Ces dernières années, des données ont mis en évidence un effet rebond après l'arrêt du médicament. C'est pourquoi l'Office fédéral de la santé publique réévalue les résultats scientifiques disponibles concernant son utilisation chez les patients ostéoporotiques. L'objectif de l'ETS (évaluation des technologies de la santé) proposée est de comparer le denosumab au placébo, aux bisphosphonates et aux modulateurs sélectifs des récepteurs aux œstrogènes sur le plan de la sécurité, de l'efficacité, du rapport coût-efficacité ainsi que des impacts juridiques, sociaux, éthiques et organisationnels, dans différents sous-groupes de patients atteints d'ostéoporose.

Une recherche bibliographique systématique a été effectuée dans huit bases de données biomédicales, en conjonction avec des registres d'essais cliniques et des sites Internet spécialisés. Sur les 9377 résultats obtenus, 74 revues systémiques ont été identifiées, à partir desquelles 21 essais contrôlés randomisés (ECR) ont été recensés et inclus. La recherche a également permis de trouver 15 études économiques répondant aux critères d'inclusion. En outre, quatre études abordaient les aspects sociaux, et quatre autres les questions organisationnelles. Les recherches de *scoping* n'ont mené à aucune publication concernant les implications éthiques ou juridiques d'une limitation du recours au denosumab (Prolia®).

Il existe suffisamment de résultats d'ECR pour procéder à une méta-analyse de la sécurité et de l'efficacité du denosumab (Prolia®) chez les femmes en post-ménopause présentant une ostéoporose et les femmes souffrant d'un cancer du sein qui suivent un traitement adjuvant par inhibiteurs de l'aromatase ; pour les deux autres sous-populations, les données disponibles sont limitées et seront donc discutées de manière narrative. Pour l'ETS, l'analyse sera stratifiée par groupes et sous-groupes de population. La conception de l'évaluation économique dépendra des meilleures données cliniques disponibles. L'approche inclura des modèles de coût-efficacité et produira un rapport coût-efficacité différentiel pour chaque élément de comparaison. Une analyse d'impact budgétaire sera également menée. Les recherches dans les bases de données n'ont permis d'identifier qu'un nombre limité d'études traitant des aspects sociaux, éthiques, juridiques et organisationnels.

Sintesi

L'osteoporosi è una malattia ossea che si manifesta con una diminuzione della densità minerale delle ossa e un aumento del rischio di frattura. Il Denosumab (Prolia è utilizzato per trattare l'osteoporosi riducendo il riassorbimento della sostanza ossea. Negli ultimi anni, l'evidenza scientifica ha indicato un effetto di ritorno dovuto a discontinuazione. Di conseguenza, l'Ufficio federale della sanità pubblica (UFSP) sta rivalutando le evidenze disponibili per il denosumab (Prolia) presso i pazienti osteoporotici. L'obiettivo del Health Technology Assessment (HTA) proposto è di confrontare la sicurezza, l'efficacia, il rapporto costo-efficacia nonché l'impatto legale, sociale, etico e organizzativo del denosumab rispetto a placebo, bifosfonati e modulatori selettivi dei recettori degli estrogeni in sottogruppi di pazienti affetti da osteoporosi.

È stata condotta una ricerca sistematica della letteratura in otto banche dati biomediche, in combinazione con i registri degli studi clinici e i siti web specializzati. Dai 9377 record ottenuti, sono state identificate 74 revisioni sistematiche, da cui sono stati scelti e inclusi 21 studi randomizzati controllati (RCT). La ricerca ha individuato 15 studi economici corrispondenti ai criteri di inclusione. Inoltre, quattro studi contenevano considerazioni sociali e altri quattro considerazioni organizzative. Le ricerche di scoping non hanno identificato alcuna letteratura relativa alle implicazioni etiche o legali della limitazione del denosumab (Prolia).

Esistono evidenze sufficienti di RCT per meta-analizzare la sicurezza e l'efficacia del denosumab (Prolia) in donne in post-menopausa con osteoporosi e in donne affette da cancro al seno sotto terapia adiuvante con inibitori dell'aromatasi; esistono poche evidenze per i restanti due sottogruppi che pertanto saranno solo commentate. Per l'HTA, l'analisi sarà diversificata per gruppi e sottogruppi di popolazione. La concezione della valutazione economica della salute dipenderà dalle migliori evidenze cliniche disponibili. L'approccio includerà modelli di rapporto costo-efficacia incrementale e produrrà un rapporto costo-efficacia per ogni fattore comparativo. Sarà inoltre condotta un'analisi dell'impatto sul bilancio. Dalle ricerche nelle banche dati è emerso un numero limitato di studi sociali, etici, legali e organizzativi.

Table of contents

List of Figures

List of Tables

Abbreviations and acronyms

AAIT	Adjuvant aromatase inhibitors therapy
AFF	Atypical femur fracture
ALP	Alkaline phosphatase (total)
B-ALP	Alkaline phosphatase (bone specific)
BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover marker
Ca^{+}	Calcium
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CINAHL	Cumulative Index of Nursing and Allied Literature
CTX/CrossLap	C-terminal telopeptide of type 1 collagen
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
DAPS	Denosumab Adherence Preference Satisfaction study
DECIDE	Determining efficacy: comparison of initiating denosumab versus alendronate
DIRECT	Denosumab fracture Intervention RandomizEd Controlled Trial
DPD/PYD:	Pyridinium crosslinks/deoxpyridionoline pyridinoline
DSA	Deterministic sensitivity analysis
DXA/ DEXA	Dual-energy X-ray absorptiometry
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public Health
FRAME	FRActure study in post-MEnopausal women with osteoporosis
FRAX	Fracture Risk Assessment Tool
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
GI	Gastrointestinal
HAT	Hormone ablation therapy
HRQoL	Health-related quality of life
HRT	Hormonal replacement therapy
HTA	Health technology assessment
HUI3	Health utilities index mark 3
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
LYG	Life year gained

NRS	Numeric rating scale
NTX	N-terminal telopeptide of type 1 collagen
OFDQ	Osteoporosis function disability questionnaire
OL	Open label
ONJ	Osteonecrosis of the jaw
OPAQ	Osteoporosis assessment questionnaire
OPG	Osteoprotegerin
OPTOQLQ	Quality of life questionnaire for osteoporosis
QALY	Quality-adjusted life year
P1NP	Procollagen type 1 N propeptide
PICO	Population, intervention, comparator, outcome
PMO	Postmenopausal osteoporosis
QoL	Quality of life
Qualeffo-41	Quality of life questionnaire of the European Foundation for Osteoporosis
QUS	Quantitative ultrasound
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCT	Randomised control trial
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SF-36	36-item short form health survey
STAND	Study of transitioning from alendronate to denosumab
SVGO	Schweizerische Vereinigung gegen die Osteoporose (Swiss Association against Osteoporosis)
TRAP	Tartare-resistant acid phosphatase
York CRD	University of York Centre for reviews and dissemination
VAS	Visual analogue scale
Vit D	Vitamin D
VRS	Verbal rating scale
WHO	World Health Organization

Objective of the HTA scoping report

The objective of the scoping report is to conduct a systematic literature search and to synthesise the available evidence base addressing the main health technology assessment (HTA) domains i.e. clinical effectiveness and safety; costs, budget impact and cost-effectiveness; and legal, social, ethical and organisational issues. The analytical methods that are to be used when an HTA is pursued are described in the present report. Based on quantity and quality of the extracted evidence the feasibility of pursuing an HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

In Switzerland, denosumab (Prolia®) is covered by mandatory health insurance for the treatment of osteoporosis in postmenopausal women, men with osteoporosis and an increased fracture risk, women with breast cancer on adjuvant aromatase inhibitor therapy (AAIT), and men with prostate cancer on hormone ablation therapy (HAT) with an increased fracture risk.

Pharmacovigilance reports in 2015 warned that discontinuation of denosumab therapy in patients with osteoporosis can lead to increased bone turnover, significant bone mineral loss (in some cases below baseline levels) and increased vertebral fracture risk. Such complications have not been observed after the discontinuation with other osteoporosis therapies due to differences in their mode of action.

Because of these safety issues and the existence of similarly effective therapeutic alternatives with fewer side effects, the Federal Office of Public Health (FOPH) wishes to re-evaluate the available evidence for denosumab in osteoporotic patients.

The planned HTA aims to perform an assessment of the safety, efficacy/effectiveness, cost, cost-effectiveness and budget impact of denosumab compared to all other available first-line osteoporosis therapies in Switzerland.

2 Research question

The aim of this scoping report is to identify relevant literature addressing the following research questions:

- What is the efficacy/effectiveness, safety, cost, cost-effectiveness and budget impact of denosumab (Prolia®) compared to bisphosphonates and selective oestrogen receptor modulators (SERMs) for the treatment of osteoporosis in postmenopausal women, women with breast cancer on AAIT, men with osteoporosis and an increased fracture risk, and men with prostate cancer receiving HAT with an increased fracture risk?
- Are there any legal, social, ethical or organisational issues associated with denosumab (Prolia®) therapy?

3 Medical background

3.1 Medical context and disease description

Osteoporosis is a bone disorder that decreases bone mass and density, generally making the skeleton fragile and increasing the risk of fracture.[1 2] It is characterised by imbalanced bone turnover. Bones go through constant cycles of formation and breakdown by cells called osteoblasts and osteoclasts, respectively. In osteoporotic patients, bones break down faster than they are formed.

Osteoporosis can be classified into two types. Primary disease generally results from ageing and is not caused by any other underlying condition.[3] Secondary osteoporosis can be caused by lifestyle factors (e.g. smoking), pharmaceuticals (e.g. corticosteroids, adjuvant aromatase inhibitors therapy, hormone ablation therapy) or underlying conditions such as hypoestrogenemia or hypogonadism.[4 5]

Osteoporosis can be of different severity depending on pre-existing or ageing issues, such as peak bone mass during adolescence, postmenopausal oestrogen deficiency intensity in women, and/or bone loss attributed to ageing. Each is associated with different mechanisms.[6] While research has yet to establish the full mechanisms behind bone loss, oestrogen deficiency appears to be linked to disease development.[4] It has also been demonstrated that bone loss can occur via systemic abnormalities (i.e. low levels of oestrogen, vitamin D and/or calcium fixation resulting in secondary hyperparathyroidism) or osteoblast dysfunction.[6-8]

3.2 Symptoms, natural course, and diagnostic pathway

Osteoporosis is associated with the following symptoms:

- back pain caused by fractured or collapsed vertebra
- significant height loss over time
- stooped posture
- increased fracture recurrence

Without treatment and preventive measures (e.g. lifestyle changes such as reducing smoking and alcohol consumption, fall prevention), the disease progresses over time by gradually reducing bone mass and density, in turn resulting in an increased number of fractures. In the absence of a fracture and other risk factors, osteoporosis can go undiagnosed.

The diagnosis of osteoporosis follows two main approaches:

- The World Health Organization (WHO) has defined criteria for the identification of osteoporosis based on bone mineral density (BMD) T-scores,[9] corresponding to the number of standard deviations (SD) between a patient‘s BMD test result and the mean BMD peak value in a cohort of healthy younger individuals.[10] T-scores are calculated based on BMD values measured by dual-energy X-ray absorptiometry (DXA) at several skeletal sites.[11] [12] The International Society for Clinical Densitometry and the WHO consider DXA of the hip or spine as the preferred measurement for the diagnosis of osteoporosis. A T-score of -2.5 is the diagnostic threshold for osteoporosis.[9] T-score or BMD measurements can be used to determine the relative risk of fracture.[9]
- The fracture risk assessment tool (FRAX) is an online tool that calculates the risk of fracture based on clinical risk factors such as age, sex, weight, height, glucocorticoid intake, smoking status, alcohol intake, medical history and femoral BMD of a given patient and returns a probable absolute fracture risk for the coming ten years.[13] FRAX results are more accurate for individual fracture assessment than T-scores alone,[13] as they encompass a range of factors in addition to BMD.[14]

In Switzerland, BMD is measured using DXA. The Schweizerische Vereinigung gegen die Osteoporose (SVGO, Swiss association against osteoporosis) reports discrepancies between BMD measured in the spine versus the femoral neck, suggesting that a correction factor be used to amend the results. In addition to BMD measurements, the SVGO recommends that a diagnosis be established based on medical history (i.e. general condition, risk factors, fracture or fall history, and illness or medications impacting bone metabolism or fall risk) and clinical examination (i.e. blood serum tests for calcium and vitamin D, decreased body mass index (BMI), indications for secondary osteoporosis, and evaluation of fall risk).[15] [16] SVGO also recommends measuring the 10-year fracture risk with FRAX. The association advises the use of adjustment factors to FRAX results depending on the dose of glucocorticoids consumed to better assess the risk of fracture in patients with probable secondary osteoporosis (***Table 3-1***).

Table 3-1 Adjustment factors for FRAX depending on glucocorticoid dosage and fracture type

Dose of glucocorticoids	Major fractures	Hip fracture
Low (<2.5mg)	-20%	-35%
Medium (2.5–7.5mg)	0%	0%
High (>7.5mg)	+15%	+20%

Source: Schweizerische Vereinigung gegen die Osteoporose [16]

3.3 Prevalence and burden of disease

Prevalence

Osteoporosis is a common disorder in the elderly population. In Switzerland, 15.1% of the population aged 50 years and above had osteoporosis in 2010, with 368,685 women and 89,862 men affected by this bone disorder and a total population at risk of 3,041,000 people.[17] [18] One third of Swiss older than 65 years are likely to experience a fall.[17] Consequently, in 2010 there were an estimated 74,000 new factures in Switzerland, with hip, spine, forearm and other fractures amounting to 14,000, 11,000, 13,000 and 36,000, respectively.[18]

Similar statistics were observed in countries neighbouring Switzerland. In France in 2010, 2,784,198 women over age 50 and 691,112 men were diagnosed with osteoporosis from 22,645,000 people in this age group, representing 15.4% of the at-risk population. Similarly, in Germany in 2010, from 33,010,000 people over age 50 there were 4,017,060 women and 1,006,652 men recorded as living with osteoporosis, representing 15.2% of the at-risk population at the time.[19] In the same year, around 22 million women and 5.5 million men within the European Union had osteoporosis, which corresponded to 3.5 million new fragility fractures, including 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million other fractures.[19]

Globally, it is estimated that over 200 million people currently have osteoporosis,[20] with one in three women and one in five men age 50 or older presenting with osteoporotic fractures.[21] It is projected that 1.6 million hip fractures occur annually worldwide, which is expected to increase to 6.3 million by 2050.[20]

Burden of disease

In general, the burden attributed to osteoporosis corresponds to an increased risk of fracture and the resulting loss of quality of life. The overall burden of disease can be measured using disability-adjusted life years (DALYs), which combine the years of life lost due to a fracture with the disability resulting from the fracture in surviving individuals. One year lost due to premature mortality equals one DALY.[22]

The burden of osteoporosis depends not only on the prevalence of the disease in any given country but also on the risk of falls in the population at risk. In Switzerland, a study aiming at demonstrating the burden of several conditions on the elderly population, highlighted that 3% of men and 5% of women had fallen in the 6 months preceding the study, with falls being more common in women over 69 years of age and in men over age 76.[23] The same study showed that, for women, the fear of falling increased drastically with age, from 4% at age 55 to 25% at age 83, compared to men at 1% at age 55 and 17%

at age 83. This difference could be explained by an increased likelihood for women to develop osteoporosis in their old age and therefore for a fall to result in a fracture.

In Switzerland, the cost of osteoporotic fractures was estimated to range from CHF34,374–38,871 (hip), CHF19,790–36,622 (spine) and CHF7,000–25,454 (wrist) depending on the age of the patients.[24] It is anticipated that the population over 50 years of age will increase by 26% in Switzerland between 2010 and 2025, resulting in a 33% increase in the total number of fractures. Consequently, the cost of osteoporosis in Switzerland, including the value of quality-adjusted life years (QALYs) lost, is forecast to reach CHF6.7 billion by 2025, representing an increase of 39% in men and 20% in women compared to 2010.[18] The variation between genders is due to a difference in total calculated QALYs lost due to fracture in men (36%) and women (18%). In the rest of Europe, osteoporosis causes the loss of 2 million DALYs each year.[19]

Globally, the economic burden of this disease is far greater than the projected financial burden of stroke, breast cancer, diabetes or chronic lung disease.[25] In 2000, 5.8 million DALYs were associated with osteoporotic fractures around the globe, representing 0.83% of the combined burden of non-transmittable diseases.[22]

3.4 Treatment pathway

Osteoporosis can be managed using pharmaceutical or non-pharmaceutical approaches or a combination of the two.[26-28]

In the absence of obvious signs of osteoporosis, the approach is to reduce the risk of developing the condition. These measures include lifestyle changes (e.g. reducing smoking and alcohol consumption) and prophylactic supplementation. Various associations around the world recommend adjusting patient nutrition to contain sufficient daily intake of calcium, vitamin D and protein.[22 29] Low BMI is associated with a higher fracture risk while obesity is linked to vitamin D deficiency, therefore maintaining a normal BMI through good nutrition and exercise is suggested. Regular exercise is also recommended because it can reduce the incidence of fractures.[29]

Non-pharmaceutical management of osteoporosis essentially consists of lifestyle changes (i.e. reduction in smoking and alcohol consumption) and fall prevention. Measures such as surface preparation or provision of a walking frame represent the primary management tools for patients presenting a low risk of fracture and/or BMD close to the normal range.[28]

For patients presenting with a low BMD or increased risk of fracture, practitioners usually recommend pharmaceutical treatment in addition to the lifestyle changes listed above.[28]

When selecting a pharmaceutical treatment, a clinician can choose between multiple drug types. These include bisphosphonates, SERMs, and denosumab (see ***Section 4.1*** *and* ***4.2***).[26 27]

4 Technology

4.1 Technology description

Denosumab (Prolia®) is a monoclonal antibody used to treat osteoporosis by inhibiting the activation of cells responsible for bone resorption (osteoclasts). Osteoporosis disturbs the process of bone remodelling by disrupting the fine balance between bone formation conducted by osteoblasts and bone breakdown conducted by osteoclasts, leading to a progressive loss of BMD. Denosumab aims to slow down osteoclast activity thereby reducing bone breakdown.[30]

Osteoclasts are activated by the binding of the receptor activator of nuclear factor kappa-B ligand (RANKL) to its receptor. Osteoblasts produce osteoprotegerin (OPG), which controls bone breakdown by interacting with RANKL, thus preventing its attachment to the receptor. Denosumab mimics the role of OPG by binding to RANKL and reducing the activation of osteoclasts.[30]

Denosumab is administered as a biannual subcutaneous injection of a 60mg/mL solution for a minimum of 3 years.[26 28] It is recommended that patients also take vitamin-D supplements when on denosumab therapy. It is important to note that the use of denosumab in Switzerland is limited to adults as the evidence for paediatric patients is insufficient.[31] Similarly, it is recommended that calcaemia is monitored closely in cases of severe kidney failure (i.e. creatinine clearance <30mL/min) or for patients undergoing dialysis.[31]

Denosumab is contraindicated in cases of hypocalcaemia (<2.1mmol/L) or in cases of intolerance or allergy to the medication components (i.e. denosumab, sodium acetate, sorbitol, polysorbate 20) (***Table 4-1***).[31] It is generally well tolerated by patients and adverse events are rare. Some side effects of denosumab therapy comprise skin infection (cellulitis) near the point of injection, back pain, arm and leg pain, urinary tract infection, constipation and rash.[32] A less common side effect is a reduction in blood calcium. Because of this, if the patient has kidney failure or is following a dialysis treatment calcaemia should be monitored closely. Finally, rare cases of osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) have been reported.

As denosumab acts as an antagonist of RANKL and is not a compound that will remain within bones or the body, the positive impact of denosumab disappears after discontinuation. Several studies looking at

the impact of denosumab discontinuation highlighted a rebound effect in which BMD drops after withdrawal of the drug, reducing to levels below baseline values.[33-35] This rebound effect creates a higher risk of vertebral fractures. For these reasons, evidence of the impact of denosumab discontinuation on BMD and general health outcomes is of key interest when evaluating the safety of this medication.

Prolia® is the only denosumab pharmaceutical available in Switzerland for the treatment of osteoporosis. Xgeva® is a denosumab formulation indicated for the treatment of patients with solid tumours presenting bone metastases or patients with bone giant-cell tumours. As it is not prescribed for the treatment of osteoporosis, this formulation was not included in the present assessment.[36 37] Dosage and indications/contraindications associated with Prolia® are summarised in ***Table 4-1***.

Table 4-1 Technology details

Name (manufacturer)	Dose and Administration	Indications	Contraindications
Prolia® (AMGEN Switzerland AG)	One 60mg subcutaneous injection administered every 6 months (thigh, abdomen or upper arm)	• postmenopausal women with T-score values ≤ -2.5 SD • supplementary to AAIT in women with breast cancer presenting an increased fracture risk • supplementary to HAT in men with prostate cancer presenting an increased fracture risk • men with osteoporosis and an increased fracture risk	Hypocalcaemia (i.e. blood calcium <2.1mmol/L) Hypersensitivity or allergy to denosumab, or the listed excipients (i.e. sodium acetate, sorbitol, polysorbate 20)

Abbreviations
AAIT: Adjuvant aromatase inhibitors therapy; **HAT:** Hormone ablation therapy; **SD**: standard deviation
Sources:
Swissmedicinfo[31]

4.2 Alternative technologies

In addition to lifestyle changes and denosumab, two classes of pharmaceuticals are currently recommended for management of osteoporosis in Switzerland. Bisphosphonates and SERMs currently available in Switzerland are summarised in ***Table 4-2.***

Bisphosphonates

Bisphosphonates represent a popular group of compounds used for the treatment of osteoporosis.[27 38] As their name indicates, they contain two phosphonates, giving them a high affinity for bone minerals through the binding to hydroxyapatite (bone mineral) binding sites. Like denosumab, bisphosphonates reduce the activity of osteoclasts, however, unlike denosumab, bisphosphonates are preferentially absorbed in active bone remodelling areas, thus a portion of bisphosphonates are retained in the newly formed bone.[39] Through these actions, bisphosphonates reduce the breakdown of hydroxyapatite within the bone, causing an overall suppression of bone resorption. Although bisphosphonates are used to treat other disorders, they are primarily used for the management of osteoporosis.[39]

In Switzerland, four classes of bisphosphonates are available: alendronate, ibandronate, risedronate and zoledronic acid (***Table 4-2***). Bisphosphonates can be administered either orally or through intravenous infusions. Alendronate is administrated orally at a weekly dose of 70mg and is available under eight different brands in Switzerland (***Table 4-2***). Similarly, risedronate (Actonel being the only brand available in Switzerland) is administered orally in the form of a 5mg pill taken daily or a 35mg pill taken weekly. Both brands of zoledronic acid commercialised in Switzerland are administered via an intravenous infusion, typically delivered as a 5mg intravenous infusion once per year. There are seven brands of ibandronate available in Switzerland, four of which are administered orally via a 150mg monthly pill and three of which are administered via a three-monthly intravenous injection containing 3mg of the active compound.

Finally, as with any medication, some patients may develop adverse events or an intolerance to bisphosphonates. One study reported adverse events in up to 62.3% of the 839 patients treated with various oral bisphosphonates and serious adverse events in 6.8% of the same cohort.[33 40] Published adverse reactions include gastrointestinal (GI) episodes in the upper and lower GI tract, infections, allergic reactions to the medication, cystitis, arthralgia, pain and fractures.[40-43] For these reasons, bisphosphonates are contraindicated for patients presenting with acute inflammation of the GI tract, oesophageal pathologies that could delay medication absorption (if taken orally), and kidney failure, or patients who have a history of allergy to the medication.

SERMs

As mentioned previously, there is growing evidence that a reduction in oestrogen production can contribute to the onset of osteoporosis.[44] SERMs act as either oestrogen agonists or antagonists in different parts of the body. It is their oestrogen agonist (i.e. compounds that can bind to oestrogen

receptors) properties that are used in the treatment of osteoporosis. A dose of SERMs mimics oestrogen thereby diminishing the impact that the reduction of this hormone has on bone turnover.[45]

There are two forms of oestrogen agonist SERMs available in Switzerland for management of osteoporosis: bazedoxifene and radoxifene. Radoxifene was the first SERM validated for the treatment of postmenopausal osteoporosis. In Switzerland, Raloxifene (Evista®) is administered orally with a daily 60mg pill. Bazedoxifene, found in Switzerland under the brand name Conbriza®, is administered as a daily 20mg pill (***Table 4-2***).[46,47] In the Swiss context, both of these medications are exclusively prescribed to postmenopausal women with a T-score ≤-1 SD or who have experienced fractures.

Other pharmaceuticals for the treatment of osteoporosis

In addition to denosumab, bisphosphonates and SERMs, practitioners can recommend several other pharmaceutical treatments for osteoporosis.

Hormone replacement therapies (HRT) are another example of antiresorptive agents that can adjust oestrogen levels and in turn inhibit the detrimental effect of menopause on bone turnover. HRT can be conducted with oestrogen with or without progesterone.[48] Estalis® is a hormone (oestradiol) currently recommended as a second-line treatment for osteoporosis (induced by oestrogen deficiency) in Swiss postmenopausal women with a high fracture risk and for women presenting oestrogen-deficiency symptoms.[49]

Some pharmaceuticals can increase bone formation or BMD, including parathyroid hormones and strontium. A commonly prescribed parathyroid hormone is teriparatide, which has shown to increase BMD significantly in postmenopausal women.[50] The use of teriparatide is limited in Switzerland to second line treatment in a) patients with glucocorticoid induced osteoporosis and high fracture risk and in b) patients with progressive osteoporosis, i.e. incident fractures during antiresorptive treatment. Strontium is not licensed in Switzerland.

Calcitonin is a hormone produced by the thyroid that helps regulate serum calcium and phosphate levels, opposing the action of parathyroid hormones. It can provide efficient but short-term pain relief in patients with osteoporotic vertebral fractures. In Switzerland, the use of calcitonin is limited to population subcategories that do not correspond to the population groups selected for this assessment.

Due to their limited use or lack of availability in Switzerland, these pharmaceuticals were not selected for the present assessment.

Table 4-2 Alternative technologies available in Switzerland

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
Bisphosphonate	Alendronate	Alendron-Mepha Lactab® (Mepha Pharma AG) Alendron D3-Mepha (Mepha Pharma) Alendronat Helvepharm (Helvepharm AG) Alendronat Sandoz® 70 (Sandoz Pharmaceuticals AG) Alendronate Spirig HC® (Spirig HealthVare AG) Alendronate Streuli® (Streuli Pharma) Binosto® (Labatec Pharma SA) Fosamax® (MSD Merck Sharp and Dohme AG) Fosavance® (MSD Merck Sharp and Dohme AG)	70mg weekly (one pill) for all alendronate medications	- postmenopausal women men - postmenopausal women or men with insufficient vitamin D (Alendron D3-Mepha)	- acute inflammation of GI tract - symptomatic osteomalacia - oesophageal pathologies preventing or delaying medication transport to the stomach - kidney failure (i.e. creatinine clearance <30ml/min) - hypocalcaemia - hypersensitivity or allergy to medication components - patients unable to maintain vertical position for at least 30 minutes
Bisphosphonate	Ibandronate (ibandronic acid)	*Intravenous injection:* Bonviva® i.v. (Future Health Pharma GmbH) Ibandronat Helvepharm (Helvepharm AG) Ibandronat-Mepha Osteo i.v. (Mepha Pharma AG) Ibandronat Spirig HC® i.v. (Spirig HealthCare AG) Ibandronat Sandoz® i.v. (Sandoz Pharmaceuticals AG)	One 3mg intravenous injection every three months	- postmenopausal women with increased vertebral fracture risk	- hypersensitivity or allergy to medication components - untreated hypocalcaemia

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
		Oral medications: Bonviva® 150mg (Future Health Pharma GmbH) Ibandronat-Mepha® 150mg (Mepha Pharma AG) Ibandronat Spirig HC® 150mg Ibandronat Sandoz® 150mg (Sandoz Pharmaceuticals AG)	150mg monthly (one pill)	- postmenopausal women with increased vertebral fracture risk	- patients with hypersensitivity or allergy to medication components - untreated hypocalcaemia - oesophageal pathologies preventing or delaying medication transport to the stomach - patients unable to maintain vertical position for at least 30 minutes
Bisphosphonate	Risedronate (sodium risedronate)	Actonel® (Future Health Pharma GmbH)	One 5mg pill per day or one 35mg pill weekly	- postmenopausal women - men with osteoporosis and increased fracture risk - patients presenting with corticosteroid-induced osteoporosis	- hypersensitivity or allergy to medication components - untreated hypocalcaemia - severe kidney failure (creatinine - clearance <30mL/min) - patients unable to maintain vertical position for at least 30 minutes - during pregnancy or lactation
Bisphosphonate	Zoledronate (zoledronic acid)	Aclasta® (Novartis Pharma Schweiz AG) Zoledronate Osteo Sandoz® (Sandoz Pharmaceuticals AG)	For osteoporosis, it is recommended to infuse a single dose of 5 mg of Zoledronate Osteo Sandoz® and Aclasta® intravenously once a year.	- postmenopausal women - men with osteoporosis and increased fracture risk - patients presenting with corticosteroid-induced osteoporosis	- during pregnancy or lactation - hypersensitivity or allergy to medication components of other bisphosphonates - hypocalcaemia (Zoledronat Axapharma Osteo 5) - severe kidney failure (creatinine clearance <35mL/min, Zoledronat Axapharma Osteo 5)

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
SERM	Bazedoxifene (bazedoxifenum ut bazedoxifeni acetas)	Conbriza® (Pfizer AG)	One 20mg pill daily	postmenopausal women with increased facture risk (-1 difference in T-score measured by densitometry in the spine or at the femoral neck)	- deep vein thrombosis in women for whom postmenopausal status is not clearly established - clinic signs of endometrium cancer - unexplained vaginal bleeds; during breast feeding - hypersensitivity or allergy to bazedoxifen or any other component of the medication
SERM	Raloxifene (raloxifene hydrochloride)	Evista® (Daiichi Sankyo (Schweiz) AG)	One 60mg pill daily	postmenopausal women with increased facture risk (-1 difference in T-score measured by densitometry in the spine or the distal area of the forearm)	- women of reproductive age - history of deep vein thrombosis - hypersensitivity or allergy to components of the medication - liver failure - severe kidney failure - unexplained uterine bleeds

Abbreviations
SERM: Selective oestrogen receptor modulators.
Source: Swissmedicinfo.ch [51]

5 PICO

5.1 PICO box

Table 5-1 Study selection criteria

P:	1. Postmenopausal women with osteoporosis (with a reduction of more than 2.5 standard deviations in osteodensitometry or in case of a fracture) 2. Women with breast cancer receiving AAIT and an increased fracture risk[a] 3. Men with osteoporosis and an increased fracture risk[a] 4. Men with prostate cancer on HAT and an increased fracture risk[a] *Exclusion criteria: Patients with multiple myeloma, bone metastases (from solid tumours), giant-cell tumours, hypercalcaemia of malignancy refractory to bisphosphonate treatment.*
I:	Denosumab (Prolia®) or denosumab (60mg) *Exclusion criteria: denosumab (Xgeva®) or denosumab (120mg)*
C:	• All bisphosphonates available in Switzerland (alendronate, ibandronate, risedronate, zoledronate) • All selective SERMs available in Switzerland (bazedoxifene, raloxifene) • Placebo
O:	**Efficacy/effectiveness:** *Primary* • Fractures e.g. lumbar spine, vertebral fractures, hip fractures (femoral neck fractures, intertrochanteric factures) • Health-related quality of life (HRQoL) e.g. mean change measured with SF-36, OFDQ, OPTOQLQ, Qualeffo-41, OPAQ etc. *Secondary* • Bone mineral density (BMD) • Bone turnover markers (BTM) – measured using CTX, NTX, DPD, ALP, B-ALP, Osteocalcin and/or P1NP • Fracture risk [a] **Safety:** • Mortality • Treatment-related adverse events • Withdrawal due to treatment-related adverse events • Adverse events upon discontinuation of denosumab e.g. rebound effect [b] **Compliance:** • Adherence to therapy [c] • Primary non-adherence/ non-fulfillment adherence [d] • Non-persistence [e] • Non-conforming [f]

Abbreviations

AAIT: adjuvant aromatase inhibitors therapy; **AFF:** atypical femur fracture; **ALP:** alkaline phosphatase (total); **B-ALP:** alkaline phosphatase (bone specific); **BMD:** bone mineral density; **CTX/CrossLaps:** C-terminal telopeptide of type 1 collagen; **DPD/PYD:** pyridinium crosslinks/deoxypyridionoline pyridinoline; **HAT:** hormone ablation therapy; **NRS**: numeric rating scale; **NTX:** N-terminal telopeptide of type 1 collagen; **OFDQ:** osteoporosis function disability questionnaire; **OPAQ:** osteoporosis assessment questionnaire; **OPTOQLQ:** quality of life questionnaire for osteoporosis**; P1NP:** procollagen type 1

N propetide; **QoL**: quality of life; **QUS**: quantitative ultrasound; **Qualeffo-41:** quality of life questionnaire of the European Foundation for Osteoporosis; **HRQoL**: health-related quality of life; **SERMs:** selective oestrogen receptor modulators; **SF-36**: 36-item short form health survey; **VAS:** visual analogue scale; **VRS:** verbal rating scale.

Explanatory notes

[a] Calculated using: age, BMD, body weight, number of falls in the last year, and number of fractures after the age of 50 etc.[52]

[b] After stopping denosumab (Prolia®) one or more of the following occurs: rate of BMD loss increases above baseline levels, increase in BTM indicates increased bone resorption (i.e. CTX, NTX, DPD), and/or increased rate of vertebral fractures.[53-55]

[c] **Adherence:** *"the degree to which the person's behaviour corresponds with the agreed recommendation from a healthcare provider", WHO*.[56]

[d] **Primary non-adherence/non-fulfillment adherence:** Where medication prescribed by the medical practitioner is never fulfilled or initiated by the patient.[57]

[e] **Non-persistence:** When a patient does not adhere to the medication regimen as prescribed due to miscommunication about the therapeutic plan. There are 2 types of non-persistence: 1) unintentional non-persistence occurs when patients are prevented from implementing the treatment regimen due to resource and capacity limitations (e.g. cost, competing demands); 2) intentional non-persistence occurs when patients do not adhere with the treatment regimen due to their own motivations i.e. attitudes, expectations, and beliefs.[57]

[f] **Non-conforming:** Where patients do not adhere to the treatment regimen as prescribed (e.g. skipping doses, taking medication at incorrect times, taking more than prescribed dose, taking incorrect doses).[57]

5.2 Population

The populations of interest reflect the current restrictions on denosumab (Prolia®) in Switzerland (per the Spezialitätenliste). These populations broadly contain patients who have either primary or secondary osteoporosis. Primary osteoporosis occurs in postmenopausal women (T-score ≤ -2.5) and men without underlying disease (i.e. cancer, hormonal disorders, etc.). Secondary osteoporosis occurs in cancer patients receiving medication – specifically, women with breast cancer receiving AAIT who have an increased fracture risk, and men with prostate cancer on HAT who have an increased fracture risk. Studies reporting only on patients with multiple myeloma, bone metastases (from solid tumours), giant-cell tumours, and/or hypercalcaemia of malignancy due to bisphosphonate treatment were excluded from this review, as these are indications for Denosumab (Xgeva®), a different formulation of the medication.

5.3 Intervention

The intervention under investigation is the drug denosumab (Prolia®), a monoclonal antibody that inhibits the attachment of RANKL to its receptors, enabling an increase in bone mass in patients. Denosumab (Prolia®) administered subcutaneously in 60mg doses will be included. Denosumab (Xgeva®) and denosumab (Prolia®) administered in 120mg doses will be excluded.[36 58]

5.4 Comparator

Three relevant comparators will be included. Bisphosphonates and SERMs are active comparators available in Switzerland. Bisphosphonates are a class of drugs that inhibit bone remodelling and are commonly used to treat osteoporosis.[59] Only the four types of bisphosphonate available in Switzerland (alendronate, ibandronate, risedronate and zoledronate) will be included. SERMs are a class of drugs that can stimulate or inhibit oestrogen receptors. SERMs are used to treat a large variety of postmenopausal-related conditions (including osteoporosis) because the drug behaves differently in various types of human tissue.[60] Only the two types of SERMs available in Switzerland (i.e. bazedoxifene and raloxifene) will be included in the evidence base. The final comparator is placebo, which will be included to evaluate the efficacy of the medication.

5.5 Outcomes

Efficacy and effectiveness outcomes

Fracture is a critical outcome. Osteoporotic fractures have a substantial impact on quality of life.[61 62 63] They result in morbidity and disability and can cause substantial pain, chronic disability and death. Hip

and vertebral fractures are the most prevalent and debilitating types of osteoporotic fractures. Hip (femoral neck and intertrochanteric) fractures can cause substantial pain and decrease mobility, which results in increasing dependence.[61 62] Vertebral (spinal compression) fractures can lead to deformity, chronic back pain, height loss, decreased mobility and decreased pulmonary function.[61 62] Fractures can have a significant impact on a patient's ability to perform daily living activities and live independently.[61-63]

Health-related quality of life (HRQoL) is also a critical outcome.[64-66] HRQoL can be measured using a patient self-reported assessment of physical, social, and emotional/ mental health. Examples of HRQoL tools used to measure the impact of primary or secondary osteoporosis on patients are Qualeffo-41 and the osteoporosis assessment questionnaire (OPAQ).[64-66] Qualeffo-41 measures pain, physical, social, and mental function as well as general health,[67] whereas OPAQ measures physical, emotional, and social functioning as well as loss of usual activities.[66]

BMD is an important outcome because it provides a vital indication of bone health via a non-invasive scan.[68] BMD measurements can be taken at multiple locations in the body but is most reliably measured at the lumbar spine, the femoral neck and the radius.[68-71] BMD scores can show whether a patient is responding to treatment, as well as assist in the calculation of a patient's fracture risk.[52 68 71-73]

Bone turnover markers (BTMs) are commonly used in clinical research to measure either bone formation (e.g. PINP, osteocalcin, B-ALP) or bone resorption (e.g. CTX, NTX, tartrate-resistant acid phosphatase, hydroxyproline), and thus determine the efficacy of a treatment (***Table 5-2***), adapted from Lane et al., 2006.[74] These markers represent the resulting metabolites of bone formation and resorption released to the blood stream. They are an important outcome as they can help determine whether a patient is responding to treatment, the impact of treatment withdrawal, or if a specific intervention is causing secondary osteoporosis.[28 75 76] As with BMD, BTMs provide a non-invasive indication of a patient's continuing bone health by blood serum or urine testing.[75-77]

Table 5-2 Common BTMs used to measure bone formation and resorption

Marker type	Present in blood serum	Present in urine
Bone formation	• B-ALP • P1NP • Osteocalcin • Propeptide of type I collagen •	Nil
Bone resorption	• TRAP • CTX • NTX	• Hydroxyproline • Pyridinolines • Deoxypyridinolines • NTX • CTX

Abbreviations
B-ALP: bone-specific alkaline phosphatase; **BTM:** bone turnover marker; **CTX:** C-terminal telopeptide of collagen cross-links; **NTX:** N-telopeptide of collagen cross-links; **P1NP:** procollagen type 1 N-terminal propeptide; **TRAP:** tartare-resistant acid phosphatase.
Note
CTX is the only BTM used in Switzerland.
Source: Lane[74]

Fracture risk is an important outcome for a patient with osteoporosis. It provides an individualised probability of a fracture occurring.[78 79] The most common tool used to calculate fracture risk is the fracture risk assessment tool (FRAX®),[52 72 79] which provides a 10-year probability for major osteoporotic fracture (i.e. fractures of the hip, spine, forearm and humerus).[80] FRAX® calculates absolute fracture risk by using both non-skeletal and skeletal risk factors. Non-skeletal factors include smoking status, BMI, vitamin D deficiency, frequency of falls past 50 years of age, physical activity, low calcium intake and excessive alcohol consumption. Skeletal factors include gender (i.e. female), postmenopausal status (i.e. started early), amenorrhoea (primary or secondary), age, ethnicity (i.e. Caucasian), low BMD, BTM (i.e. high resorption markers), long-term glucocorticoid therapy, rheumatoid arthritis, neuromuscular disorders, and hypogonadism in men (primary or secondary).[52 72 79]

Safety

Total mortality and **adverse events upon discontinuation of treatment (i.e. rebound effect)** are both critical outcomes. Total mortality will reflect if denosumab (Prolia®) has the potential to be fatal to patients,[81-83] whereas adverse events experienced upon discontinuation of denosumab (Prolia®) (i.e. rebound effect) will reflect if stopping the treatment could jeopardise patient health.[53 55 84-86] Adverse events upon the discontinuation of denosumab (Prolia®) may be defined as when one of the following occurs: rate of BMD loss increases above baseline levels, increase in BTM indicates increased bone resorption (i.e. CTX, NTX, DPD), and/or increased rate of vertebral fractures.[53 55 84 85]

Treatment-related adverse events and **withdrawal due to treatment-related adverse events** are important outcomes. These outcomes will reflect if any patients have been harmed as a result of a

denosumab (Prolia®) treatment regimen.[83 87 88] Examples of treatment-related adverse events associated with denosumab that may cause a patient to discontinue treatment include, but are not limited to: AFF; dermatological issues (e.g. dryness, peeling blisters); dental issues (e.g. decay, infection, delayed healing); ONJ; pain in muscle, joints, and/or bone; hypocalcaemia; and serious infections.[81 82 88 89]

Compliance

Compliance is a critical outcome for patients with osteoporosis being treated with an anti-resorptive therapy such as denosumab (Prolia®).[90] Primary or secondary osteoporosis is a chronic illness that needs continuous treatment to ensure long-term bone health. The key to achieving this is patient compliance with the treatment regimen.[90-92] For denosumab (Prolia®), it is paramount to ensure that patients continually take their oral medication as prescribed or that they routinely present for their scheduled 6-monthly subcutaneous injections.[58 90 92] Compliance will be measured using: adherence[A], primary non-adherence/non-fulfillment adherence[B], non-persistence[C], and non-conforming[D].

[A] *"The degree to which the person's behaviour corresponds with the agreed recommendation from a healthcare provider"*.WHO[56]

[B] Where medication prescribed by the medical practitioner is never fulfilled or initiated by the patient.[57]

[C] When a patient does not adhere to the medication regimen as prescribed, due to a miscommunication about the therapeutic plan.[57]

[D] Where patients do not adhere to their treatment regimen as prescribed (i.e. skipping doses, taking medications at incorrect times, taking more than prescribed, taking incorrect doses).[57]

6 HTA key questions

To evaluate the technology, the following key questions are addressed, covering the central HTA domains as designated by the *European Network for Health Technology Assessment (EUnetHTA) Core Model* (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, and legal, social, ethical and organisational aspects):

1. Is denosumab (Prolia®) effective/efficacious compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo in osteoporotic patients?
2. Is denosumab (Prolia®) safe compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo in osteoporotic patients?
3. What are the costs associated with denosumab (Prolia®)?
4. Is denosumab (Prolia®) cost effective compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo in osteoporotic patients?
5. What is the budget impact of denosumab (Prolia®)?
6. Are there legal, social or ethical issues associated with denosumab (Prolia®) in osteoporotic patients?
7. Are there organisational issues associated with denosumab (Prolia®) in osteoporotic patients?

6.1 Additional question(s)

1. What effect does denosumab (Prolia®) discontinuation (i.e. the rebound effect) have on osteoporotic patients?
2. Are there any compliance issues with denosumab (Prolia®) compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo?

7 Methodology literature search

7.1 Databases and search strategy

A scoping search strategy was created to identify literature that addresses the research questions. Initially, a scoping literature search was conducted to identify relevant systematic reviews on the use of denosumab (Prolia®) to treat osteoporosis. Relevant randomised controlled trials (RCTs) were identified through pearling of these systematic reviews. Additional scoping searches were designed to highlight economic, social, ethical, legal and organisational issues related to the use of denosumab.

The literature searches were conducted in eight biomedical databases (PubMed, Embase, Cochrane Library, Cumulative Index of Nursing and Allied Health Literature [CINAHL], EconLit, University of York Centre for Reviews and Dissemination (York CRD), Ethicsweb, PsychInfo) up to 22 May 2020. In addition, an updated scoping search was conducted in York CRD with a restructured search strategy (***Table 12-9, Appendix A***) on 2 October 2020. Details about the bibliographic databases are available in ***Table 12-3*** (***Appendix A***). Additionally, the websites of HTA agencies were searched to identify relevant HTA reports that included cost-effectiveness analyses (CEAs) (***Appendix A***), and clinical practice guideline repositories were searched for current clinical practice guidelines. The search strategies for RCTs and systematic reviews were verified using known publications, identified through targeted searches.

The key search terms related to the population and intervention were combined with various methodological and topical search filters (systematic review and HTA, cost-effectiveness, ethical, social, etc.), depending on the database and research question being addressed. The filters and full search strategy for each database are reported in ***Appendix A***. The search filters are presented for the PubMed database; the syntax for each filter was adapted for Embase and CINAHL (available upon request).

7.2 Other sources

Searches were conducted in five clinical trial registries to identify ongoing clinical trials related to the treatment of osteoporosis with denosumab (ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, WHO, International Clinical Trials Registry Platform, Current Controlled Trials MetaRegister, and Australian New Zealand Clinical Trials Registry). Clinical trial registries were searched using the keywords outlined in ***Table 12-4*** (***Appendix A***). Additional grey literature searches were conducted on specialty websites (***Appendix A***) to highlight any relevant literature that may not have been otherwise identified.

7.3 Study selection

Results from the literature search were imported into Rayyan (bibliographic management software). Rayyan functions similarly to Endnote but allows for easy blinding of reviewers and management of study inclusion conflicts.[93] Study selection was limited to English, French, German and Italian language studies. French, German, and Italian are three of the four official languages of Switzerland. The fourth language of Romansh was not included because of the limited number of publications available.[94] [95] Only studies that met the population, intervention, comparator, and outcome (PICO) criteria were considered eligible for inclusion. Studies based outside of WHO-Mortality-Stratum A countries were excluded during full-text screening because the cause of death and burden of disease in these countries are not comparable to Switzerland (i.e. Andorra, Australia, Belgium, Brunei, Canada, Croatia, Cuba, Cyprus, Czech Republic (Czechia), Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, The Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, UK, and USA).[96]

Study selection was conducted independently by two reviewers in duplicate, in two phases. All records were screened by title and abstract. Conflicts between reviewers on study inclusion were settled via consensus. If consensus could not be reached, a third reviewer decided whether to include or exclude the citation. Articles deemed potentially relevant were then reviewed in full text by both reviewers independently, with disagreements settled via the same procedure of consensus.

Study characteristics (e.g. author details, country of publication, year, setting, length of follow-up, population, intervention, comparator, outcomes, sample size) were extracted for the included studies using preformed extraction templates. All data extractions were completed by one reviewer, then checked by a second reviewer for accuracy.

Different types of publications and study designs were considered for selection. RCTs that met the above PICO criteria were included to assess the clinical effectiveness of denosumab (Prolia®). Due to the limited amount of evidence available for the effects of denosumab (Prolia®) discontinuation, single-arm studies that met the population, intervention, and outcomes detailed in ***Table 5-1***, were also included to assess safety. Similarly, RCTs and non-randomised studies were considered when identifying evidence for determining the cost-effectiveness of denosumab (Prolia®). Systematic reviews, literature reviews, RCTs, non-randomized studies, single arm studies, ethnographic studies, phenomenological studies, narrative research, and case studies were considered when assessing ethical, social, organisational, and legal considerations***.***

8 Synthesis of evidence base

8.1 Search results

Literature searches identified 9,377 records (***Figure 1***). Duplicates were removed (n=1,440) and 7,937 items were reviewed by title and abstract. In total, 346 studies were reviewed by full text. A complete list of articles excluded at full text review is presented in ***Appendix D***. A total of 135 publications were included, containing 74 systematic reviews (listed in ***Appendix D***). The latter were analysed for references and a total of 33 publications related to 19 individual trials were pearled from these systematic reviews.[40-42 53 97-125] Another 11 publications (n=3 trials), being single-arm RCT extensions looking at the impact of denosumab (Prolia®) discontinuation, were identified and included in the extraction.[85 126-135] Two RCTs that included a discussion of social considerations were also pearled from the systematic reviews.[42 106] Details about the specific outcomes and populations are presented below.

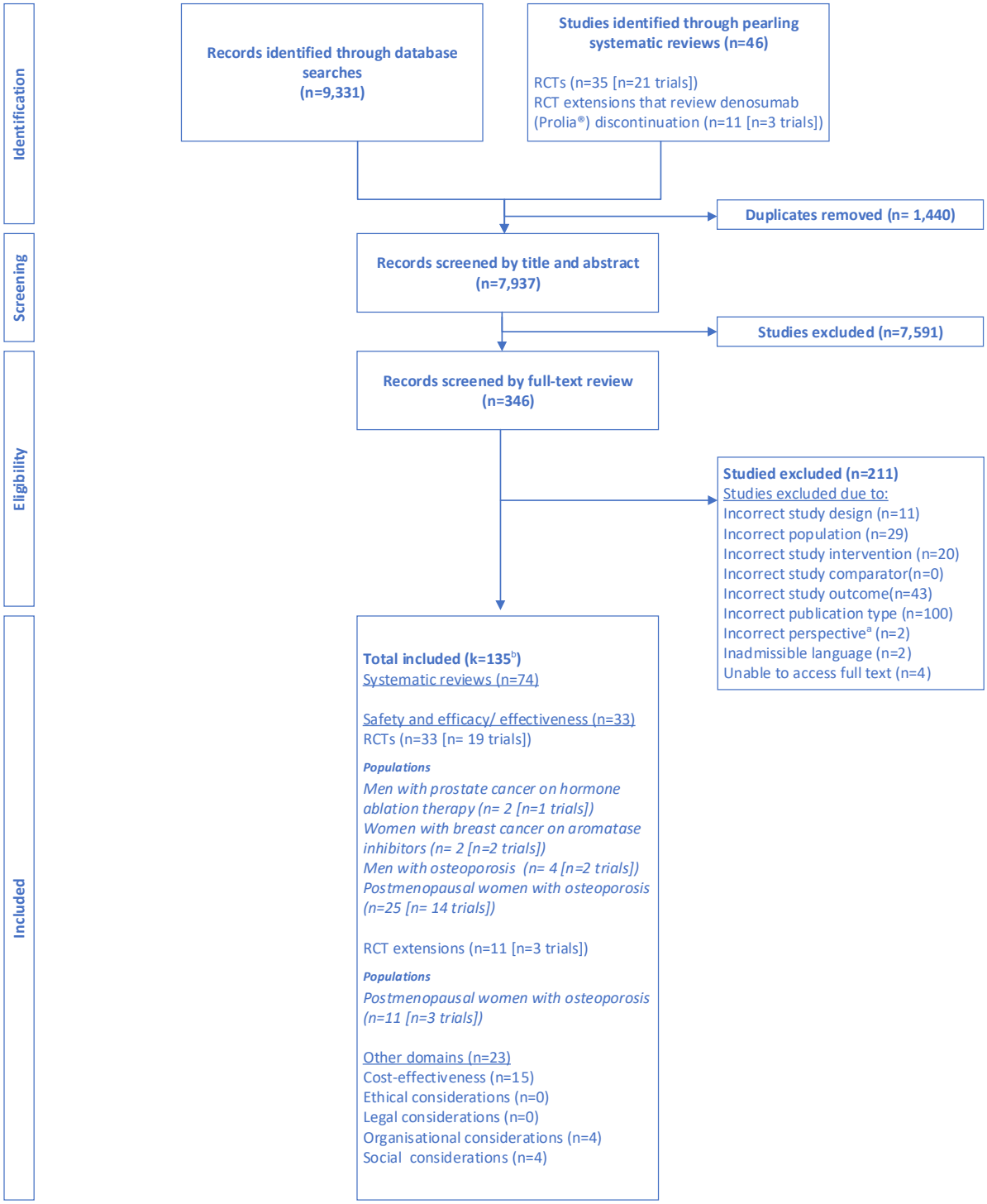

Figure 1 PRISMA Flow chart

Abbreviations

RCT: Randomised control trials

Explanatory notes

[a] Article that addresses auxiliary considerations from an investment standpoint instead of disinvestment.

[b] Some articles are included in multiple domains

8.2 Evidence base pertaining to efficacy, effectiveness and safety

8.2.1 Search results

A total of 33 publications related to 19 RCTs were extracted for clinical effectiveness and safety outcomes; 7 compared denosumab (Prolia®) to placebo (see ***Table 8-1*** below and ***Table 13-1*** in ***Appendix B***);[53 99-105 108 110 114-116 122-124] 10 compared denosumab (Prolia®) to bisphosphonates (see ***Table 8-2*** below and ***Table 13-2*** in ***Appendix B***);[40-42 97 106 107 113 117-121 125] Two compared all three treatments and are included in both ***Table 8-1*** and ***Table 8-2***.[98 109 111 112]

None of the included RCTs compared denosumab (Prolia®) to SERMs in the populations of interest. Most of the studies were prospective (n= 18 RCTs); two included post hoc analyses of trial data. Three RCTs were extended into single-arm trials, corresponding to 11 publications, which provide information on denosumab (Prolia®) discontinuation (see ***Table 8-3*** below).[85 126-135] These studies have been highlighted below, as they provide an indication of the type of evidence available for the rebound effect. The identified studies, per outcome, include:

- **Efficacy/Effectiveness**
  - 7 placebo-controlled RCTs (n=16 publications)[53 99-105 108 110 114-116 122-124]
  - 10 active-controlled RCTs (n=13 publications) (compared to bisphosphates)[40-42 97 106 107 113 117-121 125]
  - 2 active and placebo controlled RCTs (compared to bisphosphonates and placebo) (n=4 publications)[98 109 111 112]
- **Safety**
  - 7 placebo-controlled RCTs (n=12 publications)[53 99-101 103-105 108 114-116 124]
  - 8 active-controlled RCTs, (n=11 publications) (compared to bisphosphonates)[40-42 98 106 107 117-121]
  - 1 placebo and active-controlled RCT, corresponding to 3 publications (compared bisphosphonates and placebo)[109 111 112]
  - 2 RCTs (n=2 publications) and 3 single-arm trials (n=11 publications) (denosumab (Prolia®) discontinuation)[53 85 112 126-135]
- **Compliance**
  - 3 placebo-controlled RCTs (n=3 publications)[104 105 123]
  - 7 active-controlled RCTs (n=9 publications) (compared bisphosphates)[40 42 106 107 117-121]

8.2.2 Findings regarding efficacy, effectiveness and safety

Most RCTs were conducted either in North America or in Europe or as a collaboration between both areas (n=17 publications related to 11 RCTs).[42 53 97-99 103-109 111 112 115 117 123] One trial was conducted in

Japan,[114] two trials were conducted between Europe, North America and Australia (n=3 publications),[41 113 118] one trial was a collaboration between North America, South America, Europe and Asia (n=2 publications),[119 120] two trials were conducted between Europe, North America, South America and Australia (n=3 publications),[40 121 125] while another trial included New Zealand in addition to these regions (n=7 publications).[100-102 110 116 122 124]

The number of patients in the included RCTs totalled approximately 19,759. A total of 13,842 of these patients were included in the placebo-controlled trials, 5,389 were included in trials comparing denosumab to bisphosphonates and 528 patients were enrolled in trials comparing denosumab to both placebo and bisphosphonates. All studies had a follow-up period of at least 12 months, ranging from 12 to 36 months.

The majority of RCTs dealt with the treatment of primary osteoporosis (n=15 RCTs for 29 publications).[40-42 53 97-102 106-122 124 125] Most studied postmenopausal women (n=14 RCTs for 25 publications);[33 40-42 53 98-102 106 107 109-114 116-118 121 122 124 125] while two trials looked at a cohort of men with osteoporosis and an increased risk of fracture (n=4 publications).[108 115] One trial compared denosumab (Prolia®) to bisphosphonates in men using glucocorticoids (≥7.5mg/day for <3 months or ≥3 months) (n=2 publications).[119 120] Three RCTs addressed the use of denosumab (Prolia®) to treat secondary osteoporosis arising during cancer treatment; one trial (n=2 publications) evaluated osteoporosis in men with prostate cancer on HAT and two RCTs investigated a cohort of women with breast cancer on AAIT.[103-105 123]

Regarding the primary efficacy/effectiveness outcomes, 13 of the RCTs reported data on fracture, but none of the studies presented HRQoL data (see ***Table 8-1***, ***Table 8-2, Table 13-1*** and ***Table 13-2***). Most studies identified during the search reported secondary effectiveness outcomes; 18 RCTs reported BMD and 18 RCTs reported BTMs:

- BMD was commonly measured in the lumbar spine (n=17 RCTs for 24 publications),[40 42 53 97-99 101 103-109 111-115 117-120 123] the total hip (n=15 RCTs for 22 publications),[40-42 99 101 103-109 111-115 117-120 123] the femoral neck (n=13 RCTs for 17 publications),[40-42 98 103 105-108 110 113 115 117-120 123] and the third distal radius (n=11 RCTs for 15 publications).[99 103-105 107-115 119 123] Except for the latter, these bones are the recommended references for BMD measurement in the diagnosis of osteoporosis. A small number of studies (n=4 RCTs for 6 publications) reported BMD measurements in the trochanter, narrow femoral neck, femoral shaft, intertrochanter, or total trabecular, or evaluated BMD for the whole body.[98 108 109 111 115 121] One trial evaluated cortical thickness.[121]

- BTMs were also well reported in the selected RCTs (n=17 RCTs for 25 publications).[40-42 53 97 99 101 102 104 106-109 111-115 117-121 123 125] More studies included data on resorption markers than on formation markers with a majority presenting results on CTX levels (total and serum, (n=16 RCTs for 24 publications),[40-42 53 97 99 101 102 104 106-109 111-115 117-121 125] NTX (total, serum and urine, n=4 RCTs for 4 publications),[106 109 114 123] while three RCTs (n=3 publications) displayed TRAP-5b results.[99 102 123] Some studies reported on bone formation markers such as P1NP (total and serum, n=10 RCTs for 13 publications),[40 42 53 97 99 103 104 107 113 119-121 123] B-ALP (total and serum, n=3 RCTs for 5 publications),[102 109 111 112 114] and total ALP (n=1 RCT corresponding to one publication).[97] Considering that most medications try to reduce osteoclast activity, it is understandable that a larger proportion of studies would focus on bone resorption markers to evaluate drug efficacy.

In terms of safety, 16 RCTs reported on adverse events (n=26 publications),[40-42 53 99-101 103-109 111-121 124] 14 RCTs presented end-point mortality (n=24 publications),[40-42 53 99-101 103-109 111-113 115-120 124] and two reported on discontinuation (n=2 publications).[53 112] Compliance was reported in 10 RCTs (n=12 publications).[40 42 104-107 117-121 123]

8.2.3 Findings regarding the impact of denosumab (Prolia®) discontinuation (rebound effect)

The impact of denosumab discontinuation on safety outcomes is of particular interest for this assessment. During the literature searches, two RCTs (2 publications) evaluating the impact of denosumab (Prolia®) compared to placebo or bisphosphonates were identified (see ***Table 8-1*** and ***Table 8-2***).[53 112] Additionally, several studies initially identified as RCTs but corresponding to single-arm extensions of RCTs, evaluated the impact of denosumab (Prolia®) discontinuation (see ***Table 8-3***). There were three single arm trial extensions corresponding to 11 publications.[85 126-135] For example, the 'fracture reduction evaluation of denosumab in osteoporosis every six months' (FREEDOM) trial had a well-documented extension study in which cohorts of postmenopausal women around the world received either denosumab (Prolia®) or a placebo.[85 126-129 132-135] At the end of this trial, all women who agreed to participate in the extension trial received denosumab (Prolia®) every six months to evaluate what impact the difference in exposure to the drug would have on health outcomes.[85 126-129 132-135]

Except for Bone et al. 2011 and Miller et al. 2008,[53 112] which were double-blind RCTs, all publications reporting on discontinuation were open-label prospective studies conducted on postmenopausal women (including 2 RCTs reported in 2 publications, and 3 single-arm studies reported in 11 publications).[53 85 112 126-135] The number of patients in these studies totalled approximately 14,369. Only 668 of these patients participated in a double-blind RCT, the remaining 10,795 patients participated in open-label single-arm RCT extension studies. Three of included trials (n=3 publications) were conducted solely in

the USA,[112 130 131] and an additional trial (n=1 publications) was conducted both in the USA and Canada.[53] The last trial –FREEDOM extension trial (n=9 publications)-- was a collaboration between North America, Australasia (i.e. Australia and New Zealand), South America, and Europe.[85 126-129 132-135] It is important to note that one of the single-arm studies which is part of the FREEDOM extension trial was only conducted in Switzerland (population sample size n=12).[133] All of these trials (n=13 publications) reported on discontinuation.[53 85 112 126-135] All five trials presented adverse events linked to drug discontinuation (n=13 publications),[53 85 112 126-135] all trials (n=10 publications) also reported mortality data,[53 85 112 126-129 131 132 135] and only the FREEDOM extension trial (n=4 publications) reported compliance.[85 127 128 132]

There is a lack of direct comparative evidence available that addresses the rebound effect after denosumab discontinuation (n=2 RCTs for n=2 publications).[53 112] The other three publications associated with these two trials provide discontinuation rates, but no data on BMD loss or BTMs.[99 109 111] As the rebound effect is a key element of this assessment, other lower levels of evidence from non-randomised trials will likely also need to be considered in the HTA in order to comprehensively capture the effect of denosumab (Prolia®) discontinuation in osteoporotic patients. An example of a non-randomised study would be a single-arm study measuring BMD and BTM rates pre- and post-denosumab (Prolia®) treatment.[127]

Table 8-1 Outcomes reported in RCTs comparing denosumab (Prolia®) to placebo

Author/ trial	Primary effectiveness		Secondary effectiveness			Safety			Compliance
	Fractures	HRQoL	BMD	BTM	Fracture risk	Treatment-related AE	AE associated with discontinuation	Total mortality	
Men with increased fracture risk									
ADAMO trial [108 115]	✓	x	✓	✓	x	✓	x	✓	x
Women with breast cancer on AAIT									
Ellis, 2008 [104]	✓	x	✓	✓	x	✓	x	✓	✓
Gnant, 2015 [105]	✓	x	✓	x	✓	✓	x	✓	✓
Men with prostate cancer on HAT									
Egerdie, 2012 [103] and Smith, 2009 [123]	✓	x	✓	✓	✓	✓	x	✓	✓
Postmenopausal women									
FREEDOM trial [100-102 110 116 122 124]	✓	x	✓	✓	✓	✓	x	✓	x
NCT00043186 [109 111 112]	✓	x	✓	✓	x	✓	✓[&]	✓	x
NCT00091793 [53 99]	✓	x	✓	✓	x	✓	✓[&]	✓	x
Beck, 2008 [98]	x	x	✓	x	x	x	x	x	x
Nakamura, 2012 [114]	✓	x	✓	✓	x	✓	x	x	x

Abbreviations

AAIT: Adjuvant aromatase inhibitors therapy; **AE:** Adverse events; **BMD:** Bone mineral density; **BTM:** Bone turnover marker; **DIRECT:** denosumab fracture intervention randomised placebo controlled trial; **FRAME:** Fracture study in postmenopausal women with osteoporosis; **FREEDOM:** Fracture reduction evaluation of denosumab in osteoporosis every 6 months; **HAT:** Hormone ablation therapy; **HRQoL:** Health-related quality of life; **RCT:** Randomised controlled trial.

Explanatory notes

[a] Only one study reported on adverse events due to discontinuation. [#]This study does not count as an individual RCT as it was a posthoc analysis of two RCTs already included in this table.

Table 8-2 Outcomes reported in RCTs comparing denosumab (Prolia®) to bisphosphonates

Author/ trial	Primary effectiveness		Secondary effectiveness			Safety			Compliance
	Fractures	HRQoL	BMD	BTM	Fracture risk	Treatment-related AE	AE associated with discontinuation	Total mortality	
Men with increased fracture risk									
NCT01575873 trial [119 120]	✓	x	✓	✓	x	✓	x	✓	✓
Postmenopausal women									
DAPS trial [42 106]	✓	x	✓	✓	x	✓	x	✓	✓
DECIDE trial [40]	✓	x	✓	✓	x	✓	x	✓	✓
NCT00043186 trial [109 111 112]	✓	x	✓	✓	x	✓	✓[a]	✓	x
NCT00293813 trial [121 125]	x	x	✓	✓	x	✓	x	x	✓
STAND trial [107]	✓	x	✓	✓	x	✓	x	✓	✓
Anastasilakis, 2015 [97]	x	x	✓	✓	x	x	x	x	x
Beck, 2008 [98]	x	x	✓	x	x	x	x	x	x
Brown, 2014 [41]	✓	x	✓	✓	✓	✓	x	✓	x
Miller, 2016 [113]	✓	x	✓	✓	x	✓	x	✓	x
Recknor, 2013 [117]	x	x	✓	✓	x	✓	x	✓	✓
Roux, 2014 [118]	x	x	✓	✓	x	✓	x	✓	✓

Abbreviations

AE: Adverse events; **BMD:** Bone mineral density; **BTM:** Bone turnover marker; **DAPS:** Denosumab adherence preference satisfaction; **DECIDE**: Determining efficacy: comparison of initiating denosumab versus alendronate; **DIRECT:** Denosumab fracture intervention randomised placebo controlled trial; FREEDOM: Fracture study in postmenopausal women with osteoporosis; **HRQoL:** Health-related quality of life; RCT: Randomised controlled trial; **STAND**: Study of transitioning from alendronate to denosumab.

Explanatory notes

[a] Only one study reported on adverse events due to discontinuation. [#]This study does not count as an individual RCT as it was a posthoc analysis of two RCTs already included in this table.

Table 8-3 Safety outcomes reported in single-arm trial extensions

Author/ trial	Primary effectiveness		Secondary effectiveness			Safety			Compliance
	Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Postmenopausal women									
FRAME extension[130]	Data not usable [a]					n/a	✓	x	x
FREEDOM extension[85] 126-129 132-135	Data not usable [a]					n/a	✓	✓	✓
Miller, 2011[131]	Data not usable [a]					x	✓	✓	x

Abbreviations

AE: Adverse events; **BMD:** Bone mineral density; **BTM:** Bone turnover markers; **FRAME:** FRActure study in postmenopausal women with osteoporosis; **FREEDOM:** Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; **HRQoL:** Health related quality of life; **NA[a]:** Not applicable as the detailed results were published in a previous paper.

Explanatory notes

[a] The effectiveness data are not usable for this study as it changed to a single-arm study for the evaluation of the impact of denosumab discontinuation on patients (note that the effectiveness data for the FREEDOM trial are all reported in other comparative studies listed in ***Table 8-1***).

8.2.4 Ongoing clinical trials

The search of clinical trial registries identified three relevant ongoing clinical trials, summarised in ***Table 8-4***. These trials are being conducted on postmenopausal women in either the US, Australia/New Zealand or Europe. Two of them (the Australia/NZ and US trials) compare denosumab (Prolia®) to both placebo and zoledronic acid (i.e. bisphosphonate). Both trials intend to report adverse events and serious adverse events; both intend to measure BMD, while one of them also reports on BTMs. The third trial, which was completed in July 2015, compared two different denosumab (Prolia®) injection processes and is therefore only relevant for safety outcomes (although this trial completed some time ago, trial results could not be identified).

Table 8-4 List of relevant trials

Trial registry ID	Indication; Sample size	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
ClinicalTrials.gov					
NCT02753283	postmenopausal women n=201	denosumab (Prolia®) [a] and zoledronic acid	placebo or zoledronic acid	efficacy/ effectiveness BMD (total hip, lumbar spine)	active, not recruiting September 2023
Australian New Zealand Clinical Trials Registry (ANZCTR)					
372599	postmenopausal women n=30	denosumab (Prolia®) [a]	placebo or zoledronic acid	efficacy/ effectiveness BTM BMD (lumbar spine) safety AEs serious AEs	active, recruiting April 2021
EU Clinical Trials Register					
2013-001279-19	postmenopausal women n=394	denosumab CP2 60mg (Prolia®) [a]	denosumab CP4 60mga	safety AEs serious AEs	completed July 2015

Abbreviations

AE: Adverse event; **BMD**: Bone mineral density; **BTM**: Bone turnover makers.

Explanatory notes

[a] Administration route via subcutaneous injection.

[b] CP2 refers to the current subcutaneous injection process and CP4 to a new subcutaneous injection process.

8.2.5 Quality of evidence assessment

Since the intervention is a pharmaceutical, ensuring adequate allocation concealment and blinding is critical in order to avoid performance bias in participants, medical practitioners, assessors and researchers. The majority of the included studies were double-blinded (i.e. medical practitioner and patient) (28 publications). One study was single-blinded; six studies were open-label, one of which did not report blinding; and two RCTs were blinded for parts of the study and open-label for the rest. A detailed investigation of risk of bias will be conducted in the full HTA using the *Cochrane Collaboration's Risk of Bias tool for RCTs version 2.0*.[136]

8.3 Evidence base pertaining to costs, cost-effectiveness and budget impact

The literature search identified 28 potential studies relevant to the PICO criteria specified in ***Section 5***. Among the 28 studies, one duplicate was excluded,[137] and 12 were excluded after full-text review (two focused on cancer patients with bone metastases,[138] [139] one presented only descriptive analysis of medication use,[140] one examined the relationship between individual patients characteristics and post-fracture osteoporosis medication use (binary outcome), which is not a relevant outcome,[141] three focused on populations in Asia,[142-144] one used denosumab as a second-line treatment to teriparatide,[145] and four studies were excluded because they were a review of the literature with broad focus on other treatment options irrelevant to the PICO.[146-149] The literature search did not identify any study carried out in Switzerland.

8.3.1 Evidence table

In total, 15 existing economic studies were identified in the literature search. A detailed extraction table for the relevant studies is outlined in ***Table 14-1*** and ***Table 14-2*** in ***Appendix C***.

8.3.2 Findings regarding costs, cost-effectiveness and budget impact

Therapeutic options

All relevant studies compared denosumab to variations of bisphosphonates, SERMs or no treatment. One study investigated the comparative cost-effectiveness between denosumab and no treatment.[150] Four studies included all treatment options (denosumab, bisphosphonates and/or SERMs), comparing each to no treatment,[137] [151-153] and the remaining ten studies compared denosumab to bisphosphonates or SERMs.[154-163] Alendronate, risedronate and zoledronate were the most common bisphosphonate comparators reported in all 15 studies, whereas etidronate was only considered in two studies.[151] [152] One study included the SERM raloxifene as the comparator.[154]

Study perspectives

The economic evaluations in the included studies were examined from a government payer perspective in nine studies,[150 151 154-157 159 160 163] from a societal perspective in two studies,[137 158] and from a third-party payer perspective in four studies.[152 153 161 162] The government payer involves direct healthcare cost paid by the state or national health insurance, with or without out-of-pocket cost paid by patients. The third-party payer includes cost paid by private insurance with potential cost paid by either state or national government.

Populations in the models

Cohorts examined in the included studies varied by age, gender, BMD and fracture risk. Nine of the included economic evaluations directly utilised the population eligibility criteria provided in the FREEDOM trial.[150 154-159 161 163] Two other studies had eligibility criteria that differed from the FREEDOM trial.[151 152] There were also studies on men only (n=2 studies),[161 162] and on both men and women (n=2 studies).[137 153] Some studies (n=10) examined population subgroups by dividing them based on fracture risk, age and fracture history.[150-158 161] Patients over 75 years of age with T-score of -2.40 and a vertebral fracture prevalence of 40% were classified as high risk in two studies.[152 154] Different age cohorts were evaluated in four studies,[152 153 156 161] and patients with and without previous history of fractures were evaluated in three studies.[152 155 158] Two studies examined subgroups of patients who were intolerant or unable to take oral bisphosphonates due to hypersensitivity, oesophageal abnormalities or unable to stand or sit upright for more than 30 minutes.[151 154]

Table 8-5 Summary of modelling information from the included studies

Model type	CUA and CEA
Modelling techniques	Markov cohort model Markov microsimulation model Discrete event simulation model
Cycle length	6 months, 12 months
Common health state	Healthy (no fracture); hip, vertebral, wrist fractures; other fractures Cause-specific and non-cause specific death
Quality of life measures	Most commonly EQ-5D
Primary outcomes	Incremental cost per quality of life gained for CUA Incremental cost per life year gained for CEA
Sensitivity analysis	Common targets i.e. variation in drug costs, discount rates, utilities, efficacies, denosumab persistence and inclusion of adverse events and treatment discontinuation PSA used to elicit parameter uncertainties in some studies

Abbreviations

CEA: cost-effectiveness analysis, **CUA**: cost-utility analysis, **EQ-5D**: EuroQol 5 dimensions questionnaire

Explanatory Notes

EQ-5D is an analytical tool which evaluates five dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Modelling techniques

The economic modelling techniques in the included studies varied to account for economic impact driven by either individual patients or a patient cohort. Most studies (n=12 studies) adopted a cohort Markov model to perform a cost-utility analysis (CUA) or a CEA.[137 151 153-156 158-163] On the other hand, three studies utilised more flexible and complex modelling techniques, with two adopting a Markov model with patient-level microsimulation,[150 157] and the other performing a discrete event simulation model.[152] There were similarities in Markov cohort studies, with the majority (n=7 studies)[137 154 155 159 160 162 163] adopting a model built for the Swedish postmenopausal osteoporosis (PMO) population,[158] with parameter adjustments to suit the specific country. For studies engaging Markov modelling techniques (n=12 studies) with or without patient level simulations, transition probabilities are derived to enable the model to be performed.[137 151 153-156 158-163] Modelling techniques used in the included studies are summarised above (***Table 8-5***).

The number of health states in the included economic evaluations ranged from three to eleven, with eight being the most frequent (n=5 studies).[137 153 154 158 163] The most common health states were healthy (no fracture); hip, vertebral or wrist fractures; other fractures and death. The 'other fracture' health state mostly consisted of pelvis, rib, tibia or femoral fractures mostly associated with osteoporosis. In instances where the health states were greater than six, post-hip and post-vertebral fractures were considered. In estimating probabilities for major fractures, two studies used the FRAX tool,[137 153] and other studies used published data to derive transition probabilities between health states in their model.[150 151 155 157 158] Additionally, prevalence rates for fracture states for different age cohorts at a point in time were reported in three studies.[154 157 158]

In the models, patients transitioned between states (events) in a six-month or 12-month cycle. Incremental cost and health outcomes, including QALYs and life years gained (LYGs) between different treatment options were evaluated over a lifetime horizon in 13 studies,[137 150 151 153-158 160-163] and over ten years in two studies.[152 159]

Costs and resource use

For all studies, included costs can be grouped into three categories: medication costs, relevant medical services costs and adverse event management costs. Medication costs include the cost of denosumab and other treatment alternatives. Medical services costs relate to expenses from inpatient and outpatient care. Adverse event management costs relate to expenses for managing any complications arising from use of denosumab or its comparators. These costs were taken from publicly available sources such as government information outlets or private sources such as pharmaceutical companies.

All included studies had incremental cost per unit of quality of life (QoL) gained as their primary outcome. Cost per life years gained was a secondary outcome in one study.[155] EQ-5D was the quality of life measure in 12 studies,[137 150 154-163] and health utilities index mark 3 (HUI3) was the quality of life measure in one study.[154] The remaining two studies reported the QOL measure from a community health survey based on the Canadian context and from the Study of Osteoporotic Fractures.[151 152]

Outcome and cost were discounted in most of the studies – seven discounted both outcomes and costs by 3%;[152 155 156 158 160-162] two studies discounted by 5%;[154 159] one study discounted by 1.5%;[151] one study discounted by 3%.[163] Two studies discounted outcome and cost differently at 1.5% and 3%, respectively.[150 157] The two remaining studies discounted neither cost nor outcome in their evaluations.[137 153]

Addressing uncertainties

In addressing the uncertainties of the modelling results, all included studies performed sensitivity analyses of key parameters individually via deterministic sensitivity analyses (DSA) or examined variation of all key parameters simultaneously via probabilistic sensitivity analyses (PSA). DSAs were performed to elicit major drivers of the evaluation results; PSAs were performed to examine how cost-effective the models are to simultaneous variations of parameters. Cost-effectiveness acceptability curves (CEACs) were also produced in some studies to examine the likelihood of cost-effectiveness for interventions.

DSAs were mostly performed by varying drug costs, discount rates, time horizons, utilities, treatment duration and discontinuation, compliance and persistence rates, and inclusion of adverse events. PSAs, on the other hand, were performed by simultaneously varying costs, utilities, compliance and persistence rates in eight studies.[150 152 154-156 160-162] DSA results were presented using tornado diagrams and bar graphs, whereas PSAs were presented as incremental cost-effectiveness ratio (ICER) scatter plots with and without thresholds.

Assumptions made in model estimation

Assumptions about inputs related to treatment therapies and health states played an important role in the included economic evaluations. Treatment duration for denosumab and its comparators was assumed to be for either three years (n=3 studies)[150 156 157] or five years (n=12 studies),[137 151-155 158-163] however, treatment duration was assumed to taper off after stopping therapy. Discontinuation varied from one to five years with two years (n=5 studies)[151 154 160-162] and five years (n=5 studies)[137 152 153 158 163] being the most common in the base case and sensitivity analysis.

Assumptions of drug adherence and persistence rates were important in influencing the economic evaluation. Rates were assumed to drop after certain periods of time with real-world adherence and persistence rates ranging from 10% to 86% for denosumab and its comparators.[151 152 155] Denosumab adherence and persistence rates were utilised in nine,[137 151 152 157 158 160-163] and ten studies respectively,[153-155 157-163] with data mostly from the Denosumab Adherence Preference Satisfaction (DAPS) study. For the comparators, assumptions on adherence and persistence rates were made in seven studies,[137 151 152 154-156 163] with data sourced from DAPS and two published studies.[108 164]

Assumptions about adverse events were made either in the base case or sensitivity analysis. Some studies did not consider adverse events in their evaluations. Seven studies excluded adverse events from the evaluation assuming that there were no significant differences between denosumab and the comparators.[150 151 153 155-157 159] Six studies included adverse events for denosumab and the comparators in the base case,[137 152 154 160-162] two studies included adverse events only in the sensitivity analysis.[158 163]

Hip, vertebral and other fractures were assumed to lead to an increased risk of death. Excessive mortality was considered in eight studies (n=8 as base-case, n=3 in DSA). Elevated mortality estimates, which varied from 10% to 30%, were either directly sourced from clinical trials or derived from the literature.[137 150 153 157 158 160 161 163]

Utilities for patients with osteoporosis were assumed to be different from the general population and among fracture health states. Different fractures were subjected to different reductions in utility values. Two methods were applied to account for the utility changes due to the disease and different fractures. Utility multipliers were derived from systematic reviews, and published and unpublished studies based on available clinical evidence or clinical assumptions. The multipliers assume a multiplicative effect due to various fractures, and they are applied to the baseline quality of life to derive the consequence utility values after the fracture.[165-173] Utility decrements are also used to account for utility loss in the included studies. Disutilities in the first and subsequent years were assumed for hip and vertebral fractures in nine studies,[137 152 154-156 159-162] but only in the first year for all fractures (hip, vertebral, wrist and other fractures) in two studies.[150 157] Additionally, disutility after the first year was assumed to reduce by 50% if there is a repeat fracture in the same site in two studies.[150 157] ‘Other fractures’ were assumed not to have an impact on QoL after the first year in five studies.[150 157 160-162]

Cost-effectiveness outcome in the Swiss context

The included studies provided relevant information on the cost-effectiveness of denosumab compared to bisphosphonates and SERMs for the treatment of osteoporosis. Existing models have provided ample information on model structures, inputs and plausible modelling techniques. These published models can be used to guide the construction and evaluation of a health economic evaluation for denosumab.

The population in the included studies focused on postmenopausal women with osteoporosis and men with osteoporosis and an increased fracture risk.[137] [150-163] One study accounted for breast cancer patients by introducing raloxifene for women who were contraindicated to bisphosphonates.[154] This means there are no studies on women with breast cancer receiving treatment with aromatase inhibitors and men with prostate cancer on hormone ablation with an increased fracture risk. Nonetheless, the evaluation outcomes of the existing economic models may be relevant to this HTA to answer how cost-effective denosumab is compared to bisphosphonates, SERMs and placebo in osteoporotic patients, and breast and prostate cancer patients at increased fracture risk. Although not included as an eligible primary study in the economic evidence base, a review by Hiligsmann et al. (2015) reported that the cost-effectiveness of osteoporosis treatments is impacted by fracture risk, medication adherence, persistence and country-specific factors.[148]

In 73% (11 of 15) of the included economic evaluations, denosumab demonstrated a cost-effective outcome below the willingness-to-pay threshold.[150] [152] [154-158] [160-163] This finding is similar to a recent review by Morizio et al. (2018), who found 79% of ICER scenarios to be below US$100,000 (2017 US$).[149] Although the existing models had a relatively consistent finding regarding the cost-effectiveness outcome of denosumab, the results of these studies also highlighted that reimbursement schemes and different patient-specific factors can influence the cost-effectiveness result of denosumab.

It is also important to note that none of these economic evaluations were conducted in the context of the Swiss health system, and not all took the health system as their evaluation perspective (societal perspectives were used in some studies.[137] [151] [158] Further, for studies taking the health system perspective in their evaluations, significant differences in health system public reimbursement implementation in different countries where the model was designed and evaluated may still cause the evaluation results to be incompatible with the Swiss system. This is particularly prominent around how medications and health services are costed in the health economic evaluations.

Two of the included studies incorporated into their economic evaluations recommendations from a recent expert consensus meeting organised by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF).[151] [152] The consensus suggested that the economic benefit of

osteoporosis medications was greatly influenced by adherence and persistence of the medication. The outcome of the meeting also put forward a number of recommendations for conducting robust and policy-relevant economic evaluations for osteoporosis treatment.

Therefore, the existing models might have significant limitations in how their model assumptions around adherence and persistence could be applied to the Swiss context.

8.4 Evidence base pertaining to legal, social and ethical issues

8.4.1 Legal issues

Searches did not identify any literature related to the legal implications of limiting denosumab (Prolia®).

8.4.2 Social issues

There is limited evidence (n=4) on social issues related to denosumab (Prolia®) and the active comparator of bisphosphonates or SERMs in osteoporotic patients. Two RCTs investigated patient experience (i.e. satisfaction and beliefs about medications),[42 106] and two were review articles.[174 175] The results indicated that patients significantly preferred biannual subcutaneous denosumab (Prolia®) injections over a daily oral bisphosphonate treatment regimen.[42 106 174 175]

Should denosumab (Prolia®) be limited, patients would have to use bisphosphonates or SERMS to treat their osteoporosis. These treatments have shorter intervals between doses and are generally taken orally. This could result in a negative patient experience and a corresponding drop in adherence. For example, in Kendler et al. (2011) patients on the oral bisphosphonate alendronate had a lower adherence (76.6%) over 12 months compared to subcutaneous injections of denosumab (Prolia®) (87.3) every 6 months.[106]

8.4.3 Ethical issues

Searches did not identify any literature related to the ethical implications of limiting denosumab (Prolia®).

8.5 Evidence base pertaining to organisational issues

Four studies investigated potential organisational issues related to limiting denosumab (Prolia®);[174-177] Three studies were review articles,[174-176] while one was a mixed-methods study.[177]

The main organisational issues that may arise if denosumab (Prolia®) is limited relate to patient experiences with the alternative treatments of bisphosphonates and SERMs (detailed in ***Section 4.2***).

As explained above, if denosumab (Prolia®) was to be limited, the benefit of a long interval between doses (i.e. biannual) would likely be replaced by a daily, weekly or monthly (i.e. short interval) bisphosphonate or SERM treatment regimen.

If osteoporotic patients are to be treated with bisphosphonates or SERMs, improved communication between medical practitioners (i.e. doctors, nurses, dentists) is paramount, in addition to in-practice patient education to improve patient adherence.[174-176] Improved education of non-specialised medical practitioners to provide continuity of care and advice could simplify, streamline and improve patient care.[174 176 177]

9 Feasibility HTA

Clinical evaluation

- Postmenopausal women

A large evidence base for postmenopausal women was identified in the scoping report for several primary and secondary effectiveness and efficacy as well as for safety outcomes (n=16 RCTs for 27 publications). Indeed, overall fractures, BMD and BTMs were well reported for this population. In terms of safety outcomes, both adverse events and mortality were well reported for postmenopausal women. Compliance was also measured in almost half of the RCTs conducted on this sub-population (n=10 RCTs for 12 publications). There is sufficient evidence to conduct a meta-analysis of RCTs comparing denosumab (Prolia®) to placebo, or bisphosphonates in postmenopausal women. No HRQoL data are currently available for this population group. There were no studies directly comparing denosumab to SERMs in this population.

- Men with increased risk of fracture

There were few comparative trials identified for denosumab (Prolia®) in men with an increased fracture risk (n=1 study for placebo with 242 patients, and n=1 study for bisphosphonates with 795 patients). There were no studies directly comparing denosumab to SERMs in this population. Neither of the included trials reported fracture risk, HRQoL, or adverse events associated with discontinuing denosumab therapy. Compliance was evaluated in one study (vs bisphosphonates). Due to the limited number of studies within this population there is insufficient evidence to conduct a meta-analysis comparing denosumab (Prolia®) to placebo, or bisphosphonates. Therefore, the results will be summarised narratively.

- Women with breast cancer on AAIT

Limited comparative evidence was identified for denosumab (Prolia®) in women with breast cancer on AAIT (n=2 RCTs) compared to placebo, and no studies compared to bisphosphonates or SERMs. The identified studies included a combined sample of 3,677 patients. Both studies presented data for fractures, BMD, adverse events, mortality and compliance. Fracture risk was not evaluated and BTM results were available for one of the two studies. No HRQoL data are currently available for this population group. There is sufficient evidence to conduct a meta-analysis comparing denosumab (Prolia®) to placebo. In addition, the results will be summarised narratively if required.

- Men with prostate cancer on HAT

There was a single comparative trial available for denosumab (Prolia®) compared to placebo in men with prostate cancer on HAT (n=1 RCT with a sample size of n=1,624). No data was identified comparing denosumab to active comparators (i.e. bisphosphonates or SERMs) in this population. No HRQoL data are currently available for this population. Therefore, a meta-analysis comparing denosumab (Prolia®) to placebo cannot be conducted as there is insufficient evidence, with only one trial being available. Therefore, the results will be summarised narratively.

Denosumab (Prolia®) discontinuation

Two RCTs presented data on adverse events caused by the discontinuation of denosumab (Prolia®); one comparing denosumab (Prolia®) to placebo and the other to bisphosphonates and placebo. As such, there is sufficient evidence to perform a limited meta-analysis comparing denosumab (Prolia®) to placebo, but not bisphosphonates. Additionally, several trials, which were RCTs during their treatment phase, studied the impact of denosumab (Prolia®) discontinuation in the long term through single-arm studies (n=3 trials for 11 publications). Considering the limited number of RCTs, lower levels of evidence (i.e. non-randomised studies and/or single arm studies) will likely need to be sought to inform this outcome in the HTA.

Economic evaluation

Based on the review of existing models, it is feasible to conduct an independent health economic evaluation to investigate the cost-effectiveness of denosumab for osteoporosis patients specifically under the Swiss context. Sufficient information is available from the published studies to guide the design of the health economic model structure. A cost-effectiveness model is likely to be undertaken based on existing literature examples. The model will be considered to specifically fit the context of Swiss health system surrounding assumptions of the model (e.g. adherence/persistence, drug discontinuations, etc.), costs, and population characteristics. Budget impact analysis can be conducted to investigate the impact of limiting denosumab on the Spezialitätenliste.

Social, legal, ethical and organisational evaluation

There is limited evidence of organisational (n=4) and social (n=4) issues related to denosumab. Contrastingly, no studies related to the ethical or legal issues associated with limiting denosumab (Prolia®) were identified. Additional non-systematic searches will be conducted at the HTA phase to ensue all appropriate literature has been identified.

Conclusion

There is sufficient evidence to undertake an HTA on the use of denosumab (Prolia®) to treat osteoporosis. There is sufficient RCT evidence to meta-analyse the safety and efficacy/effectiveness of denosumab in postmenopausal women with osteoporosis, and women with breast cancer on AAIT. However, there is limited data for the other two populations; therefore, the available evidence will be summarised narratively for these groups. There is no direct RCT data comparing denosumab with SERMs in any population. Finally, there is limited evidence on adverse events due to treatment discontinuation. Lower level evidence will be appraised for this outcome in the full HTA.

10 Outlook

Clinical evaluation

Where there is sufficient data, the clinical assessment will include a meta-analysis of published RCTs comparing denosumab (Prolia®) to either placebo or bisphosphonates. The meta-analysis will separately evaluate the eligible populations described in the PICO that have sufficient supporting evidence, and may include available pharmacovigilance data (where available). It is worth noting that the limited information available on most pharmacovigilance websites generally makes the data acceptable for patient use but not necessarily for research purposes so it may not always be appropriate for inclusion in the HTA. In addition, where sufficient data is available in RCTs, subgroup analysis will include:

- Glucocorticoids usage, particularly in men with an increased risk of fracture
- Smoking status

Where there is insufficient data to perform a meta-analysis, a narrative description of the relevant studies will be performed. Lower levels of evidence will be used to describe the impact of denosumab (Prolia®) discontinuation and in the case of identified outcome or data gaps.

Due to the absence of direct RCT evidence comparing denosumab (Prolia®) to SERMs in any population, this comparison is not able to be evaluated using direct evidence. If this comparison is of value to inform a policy decision on the continued reimbursement of denosumab, then this comparison will need to be evaluated using another method, e.g. network meta-analysis. This will consequently require additional time and resources to conduct.

Economic evaluation

Despite the ample published models available in the evidence base, it is considered necessary to undertake an independent economic evaluation due to the significant limitations of applying evaluation results and modelling approaches from the existing models to the Swiss context. Various assumptions specific to the Swiss context and health system, such as drug adherence/persistence and discontinuations, as well as the costing structure of any therapeutic options, would need to be considered during the independent economic evaluation. The detailed design, construction and evaluation of the health economic investigation of denosumab would be guided by the results of the clinical evaluation and the existing models reviewed and summarised above.

The proposed economic evaluation will not deviate significantly from the published ones in terms of the basic structures and techniques. Based on the approach of the included studies from the literature review, the economic evaluation is likely to be cost-effectiveness models to produce ICERs for each comparison between denosumab and its comparator to identify the most cost-effective treatment option. Modelling techniques for the HTA will be guided by the best available evidence. Model inputs will be informed by the results from the clinical evaluations using recent clinical data. Costs data will be sourced from the Swiss Tarif System TARMED for outpatient care, diagnosis-related groups (DRGs) for inpatient care, and the Speciality List (Spezialitätenliste) for pharmaceutical interventions. If this information is unavailable from published sources, clinical expert advice will be sought. Assumptions to be made would be investigated via sensitivity analysis, and the most likely HRQoL measure would be the EQ-5D. A budget impact analysis will be conducted with Swiss epidemiology and demographic data and an appropriate prediction model.

Social, legal, ethical and organisational issues

Key social and organisational issues and any legal or ethical considerations will be narratively summarised based on peer reviewed published literature only. Where systematic literature searches fail to capture the appropriate information, the evaluation will highlight key uncertainties and gaps around these related domains.

Additional consideration

Since the completion of the searches in May 2020 a comprehensive HTA report (including a network meta-analysis) by Davis et al. (2020) on the use of denosumab (Prolia®), raloxifene, romosozumab, and teriparatide to prevent osteoporotic fragility fractures in the UK has been published (June, 2020).[178] The HTA is detailed and meets several elements of the PICO criteria for this scoping report (***Table 5-1***). Thus, it may be possible to utilise some elements of Davis et al. (2020) in a full HTA on the treatment of osteoporosis with denosumab (Prolia®) in a Swiss healthcare context.[178] A decision on the applicability of the findings from Davis et al. (2020) to the Swiss context will be made during the HTA phase.[178]

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12 Appendix A

12.1 Literature sources

Table 12-1 Biomedical bibliographic databases

Source	Results
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Embase	https://www.embase.com/
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/
CINAHL	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete
York CRD	https://www.crd.york.ac.uk/CRDWeb/
Econlit	https://www.aeaweb.org/econlit/
PsychInfo	https://www.apa.org/pubs/databases/psycinfo/
EthicsWeb	http://www.ethicsweb.eu/search_ets

Table 12-1 HTA agency websites

Source	Location
International	
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	https://www.euroscan-network.global/index.php/en/47-public-features/761-database-home
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Australia & New Zealand	
Health Technology Reference Group (HTRG)	https://www.coaghealthcouncil.gov.au/AHMAC/Health-Technology-Reference-Group
Austria	
Austrian Institute of Technology Assessment (AIHTA)	https://www.oeaw.ac.at/ita/publikationen/
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Evidence Development and Standards Branch (HQO)	http://www.hqontario.ca

Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
Finnish Medicines Agency (FIMEA)	http://www.fimea.fi
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT)	http://cedit.aphp.fr/
Germany	
Institut für Qualität und Wirtschaftlichtkeit im Gesundheitswesen (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPH)	http://www.fhi.no/
Singapore	
Agency for Care Effectiveness (ACE)	http://www.ace-hta.gov.sg/
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency (AETSA)	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/

Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html

Source

Based on registered INAHTA agencies located in *WHO-Mortality Stratum A* countries.[96]

Table 12-2 Specialty websites

Source	Location
Geriatric	
European Geriatric Medicine Society	https://www.eugms.org/home.html
Australia and New Zealand Society for Geriatric Medicine	http://www.anzsgm.org/
Swiss Geriatric Society / Schweizerische Fachgesellschaft für Geriatrie)	https://www.sfgg.ch/
Orthopaedic	
European Society of Sport Traumatology, Knee Surgery, and Arthroscopy (ESSKA)	https://www.esska.org/page/About_Us
Nordic Orthopaedic Federation	https://www.norf.org/
American Orthopaedic Association	http://www.aoassn.org/aoaimis/aoanew
American Academy of Orthopaedic Surgeons	https://www.aaos.org/
Australian Orthopaedic Association	https://www.aoa.org.au/
Australian Society of Orthopaedic Surgeons	http://www.asos.org.au/
Belgian Orthopaedic Trauma Association	http://www.botatrauma.be/
British Orthopaedic Association	https://www.boa.ac.uk/
Czech Society for Orthopaedic and Traumatology	https://en.csot.cz/
Danish Orthopedic Society	https://www.ortopaedi.dk/
Deutsche Gesellschaft für Orthopädie und Unfallchirurgie (DGOU) / German Society for Orthopaedic and Trauma	https://dgou.de/en/home/
Sociedad Española De Cirugía Orthopédica Y Traumatología / Spanish Society of Orthopaedic Surgery and Traumatology	https://www.secot.es/
Société Française de Chirurgie Orthopédique et Traumatologique	http://www.sofcot.fr

Source	Location
Hellenic Association for Surgical Orthopaedics & Traumatology	http://eexot.gr/
Società Italiana Di Ortopedia E Traumatologia / Italian Society of Orthopaedics and Traumatology	https://siot.it/about-siot/
Irish Institute of Trauma and Orthopaedic Surgery (IITOS)	https://www.iitos.ie/
Nederlandse Orthopaedische vereniging (NOV) / Dutch Orthopedic Association	https://www.orthopeden.org/
Svensk Ortopedisk Förening / Swedish Orthopaedic Association	http://www.ortopedi.se/index1.asp?siteid=1&pageid=1
Suomen Orthopediyhdistys / Finnish Orthopaedic Association (FOA)	http://www.soy.fi/index.php?page=1340&lang=1
Swiss Orthopaedics	http://www.swissorthopaedics.ch
Osteoporosis	
International Osteoporosis Foundation	https://www.iofbonehealth.org/
European Society for Clincal and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases	http://www.esceo.org/
Osteoporosis Australia	https://www.osteoporosis.org.au/
Australian and New Zealand Bone and Mineral Society	https://www.anzbms.org.au/Index.asp
Austrian Society for Bone and Mineral Metabolism	https://www.oegkm.at/
Osteoporose Selbsthilfe Österreich / Osteoporosis self-help Austria	https://www.osteoporose-selbsthilfe.org/
Belgian Bone Club	http://www.bbcbonehealth.org/
Croatian Osteoporosis Society	http://www.osteoporoza.hr/
Cyprus Society Against for Osteoporosis	http://www.osteoporosis.org.cy
Czech Society for Metabolic Bone Diseases (SMOS)	http://www.smos.cz
Danish Bone Society	http://www.dkms.dk/
National Osteoporosis Foundation Denmark	http://www.osteoporoseforeningen.dk
Finish Bone Society	http://www.finnishbonesociety.org/
Finish Osteoporosis Association	http://www.osteoporoosiliitto.fi/
Research and Information Group on Osteoporosis (GRIO) (France)	http://www.grio.org
Bundesselbsthilfeverband für Osteoporose e.V. / Federal Self-Help Association for Osteoporosis (Germany)	https://www.osteoporose-deutschland.de/
Netzwerk-osteoporose e.V. / Osteoporosis Network (Germany)	https://www.netzwerk-osteoporose.de/
Osteoporose Selbsthilfegruppen Dachverband e.V. / Osteoporosis Self-help Groups Umbrella Organisation (Germany)	https://www.osd-ev.org/
Hellenic Osteoporosis Foundation (HELIOST)	http://www.heliost.gr
Hellenic Society for the Study of Bone Metabolism	http://www.eemmo.gr
Beinvernd / Icelandic Osteoporosis Foundation	http://www.beinvernd.is
Irish Osteoporosis Society (IOS)	http://www.irishosteoporosis.ie
Fondazione Italiana Ricerca Osteoporosi e Malattie Muscolo Scheletriche / Italian Foundation for Osteoporosis and Skeletal Muscle Diseases	http://www.firomms.it
Fondazione Italiana per la Ricerca Sulla Malattie Ossea / Italian Foundation for Research on Bone Disease	https://www.fondazionefirmo.com/
Federazione Italiana Osteoporosi e Malattie dello Scheletro / Italian	https://www.fedios.org/

Source	Location
Federation of Osteoporosis and Disease of the Skeleton	
Societa Italiana Osteoporosi e Malattie Metabolismo Minerale E Scheletrico (SIOMMMS) / Italian Society of Osteoporosis and Diseases Mineral and Skeletal Metabolism	https://www.siommms.it/
Osteoporose Stichting / Osteoporosis Foundation (The Netherlands)	http://www.osteoporosestichting.nl/
Osteoporosis Vereniging / Osteoporosis Association (The Netherlands)	http://www.osteoporosevereniging.nl
Osteoporosis New Zealand Inc.	http://www.osteoporosis.org.nz
Associação Nacional contra a Osteoporopse / National Association Against Osteoporosis (Portugal)	http://www.aporos.pt/
Portuguese Society of Osteoporosis and other Metabolic Bone Diseases (SPODOM)	http://www.spodom.org
Slovene Osteoporosis Patient Society	http://www.osteoporoza.si
Sociedad Espanola de Fracturas Osteoporoticas (SEFRAOS) / Spanish Society of Osteoporotic Fractures	http://www.sefraos.es
Fundacion Hispana de Osteoporosi Y Enfermedades Metabolicas Oseas (FHOEMO) / Hispanic Foundation of Osteoporosis and Bone Metabolic Disease (Spain)	https://www.iofbonehealth.org/societies-country-index-view/1198
Asociacion Espanola Contra La Osteoporosis (AECOS) / Spanish Association Against Osteoporosis	http://www.aecosar.es/
Osteoporosforbundet (Sweden)	https://www.osteoporos.org/
OsteoSwiss	osteoswiss.ch/de/
Schweizerische Vereinigung gegen die Osteoporose / Swiss Association Against Osteoporosis	http://www.svgo.ch/
Royal Osteoporosis Society	https://theros.org.uk/
National Osteoporosis Foundation (USA)	https://www.nof.org/
American Bone Health	https://americanbonehealth.org/
Rheumatic disease	
International League of Associations for Rheumatology (ILAR)	http://www.ilar.org/
Asia-Pacific League pf Association for Rheumatology (APLAR)	http://www.aplar.org/
European League Against Rheumatism (EULAR)	https://www.eular.org/index.cfm
Swiss Clinical Quality Management in Rheumatic Diseases (SCQM)	https://www.scqm.ch/en/ueber-uns/
Groupe des Rhumatologues Genevois (Geneva Rheumatologists Group)	http://www.rhumage.ch/
Institute of Arthritis Research (iAR):	https://www.irr-research.org/home.html
Rheumasearch Foundation	http://www.rheumasearch.ch/
Swiss Clinical Quality Management in Rheumatic Diseases	https://www.amge.ch/
Association Suisse des Polyarthritiques (Swiss Polyarthritis Association)	http://www.arthritis.ch/
Rheumaliga Schweiz (Swiss Association for Rheumatology Patients)	https://www.rheumaliga.ch/
Rheuma-Suisse	http://www.rheuma-schweiz.ch/
Swiss Society of Rheumatology (SGR) (Schweizerische Gesellschaft für Rheumatologie)	https://www.rheuma-net.ch/de/

Source	Location
American College of Rheumatology	https://www.rheumatology.org/
Australian Rheumatology Association	https://rheumatology.org.au/
Royal Australasian College of Physicians (RACP)	https://www.racp.edu.au/
Main Dans la Main Ensemble Contre Les Rhumatismes (Belgium)	https://r-humatismes.be/fr
British Society for Rheumatology	https://www.rheumatology.org.uk/
Croatian Society for Rheumatology	http://www.reumatologija.org/engKongresi_list.aspx
Croatian League Against Rheumatism	http://www.reuma.hr/
Association Française de Lutte Anti Rhumatisme (AFLAR) (France)	http://www.aflar.org
Institute of Rheumatology Research (IRR) (Germany)	https://www.irr-research.org/de/
Irish Society for Rheumatology	https://www.isr.ie/
Societa Italiana di Reumatologia/ Italian Society of Rheumatology	https://www.reumatologia.it/
Arthritis and Rheumatism Association Malta	https://www.aramalta.com/
National Association ReumaZorg Nederland (The Netherlands)	https://reumazorgnederland.nl
ReumaNederland (The Netherlands)	https://reumanederland.nl/
NorArthritis – The Norwegian Arthritis Registry	https://helse-bergen.no/en/avdelinger/revmatologisk-avdeling/norartritt
Registo Nacional de Doentes Reumáticos (Portugal)	http://www.reuma.pt/enreuma_pt.html
Spanish Society for Rheumatology	http://www.ser.es
Reumatikerförbundet (Sweden)	https://reumatiker.se/
Menopause	
International Menopause Society	https://www.imsociety.org/menopause_perspectives_around_the_world.php
Australasian Menopause Society	https://www.menopause.org.au/
European Menopause and Andropause Society	https://www.emas-online.org/
North American Menopause Society	https://www.menopause.org/home
Belgium Menopause Society	https://menopausesociety.be/en
British Menopause Society	https://thebms.org.uk/
Česká Menopauzální a Andropauzální Společnost / Czech Menopause and Andropause Society	http://www.meno-andro.cz/en/about-us
Groupe Etude de la Ménopause et du Vieillissement Hormonal (GEMVI) / Menopause and Hormonal Aging Study Group (France)	http://www.gemvi.org/
Deutsche Menopause Gesellschaft / German Menopause Society	http://www.menopause-gesellschaft.de/
Hellenic Society of Climacterium and Menopause (Emmino)	https://emmino.gr/en/
Societa Italiana della Menopausa (SIM) / Italian Society of Menopause	http://simenopausa.it/
De Menopauze Specialist / Dutch Menopause Society	https://demenopauzespecialist.nl/
Asociacion Espanola para el Esudio fde la Menopasuia (AEEM) / Spanish Association for the Study of Menopause	https://aeem.es/
Swiss Menopause Society / Schweizerische Menopausengesellschaft	https://meno-pause.ch
Endocrinology	

Source	Location
International Society of Endocrinology	https://www.isendo.org/
European Society of Endocrinology	https://www.ese-hormones.org/
Federation of International Nurses in Endocrinology (FINE)	https://finenurses.org/
International Coalition of Organisations Supporting Endocrine Patients (ICOSEP)	https://icosep.org/
Endocrine Society	https://www.endocrine.org/about-us
Hormone Health Network	https://www.hormone.org/about-us
American Association of Clinical Endocrinologist	https://www.aace.com/
Endocrine Society of Australia	https://www.endocrinesociety.org.au/
Belgian Endocrine Society	https://endocrinesociety.be/
Deutsche Gesellschaft fur Endokrinologie / German Society for Endocrinology	https://www.endokrinologie.net/
Hellenic Endocrine Society-Panhellenic Association of Endocrinologists	http://www.heliost.gr
Hellenic Endocrine Society	http://www.endo.gr/
Société Française d'Endocrinologie / French Society of Endocrinology	http://www.sfendocrino.org/
Suomen Endokrinologiyhdistys r.y./ Finnish Endocrine Society	https://www.endo.fi/
Dansk Endokrinologisk Selskab / Danish Endocrine Society	http://www.endocrinology.dk/
Hrvatsko društvo za endokrinologiju i dijabetologiju / Croatian Society for Endocrinology and Diabetology	http://www.hded.com.hr/
Österreichische Gesellschaft für Endokrinologie und Stoffwechsel / Austrian Society for Endocrinology and Metabolism	http://www.oeges.at/
Swiss Society for Endocrinology and Diabetology	https://www.sgedssed.ch/
Svenska Endokrinolog Föreningen / Swedish Endocrine Society	https://endokrinologforeningen.se/
Sociedad Española de Endocrinologia y Nutrición / Spainsh Society for Endocrinology and Nutrition	https://www.seen.es/inicio.aspx
Society for Endocrinology (UK)	https://www.endocrinology.org/
Združenje Endokrinologov Slovenije / Slovenian Endocrine Society	https://endodiab.si/
Sociedade Portuguesa de Endocrinologia Diabetes e Metabolismo / Portuguese Society of Endocrinology, Diabetes and Metabolism	http://www.spedm.pt/
Nederlandse Vereniging Voor Endocrinologie / Netherlands Society for Endocrinology	https://www.nve.nl/openbaar/algemeen2
Società Italiana Endocrinologia / Italian Endocrine Society	http://www.societaitalianadiendocrinologia.it/html/cnt//home.asp
Associazione Medici Endocrinologi / Endocrinologist Medical Association	http://www.associazionemediciendocrinologi.it/
Irish Endocrine Society	https://irishendocrinesociety.com/
Cancer	
International Agency for Research on Cancer (IARC)	https://www.iarc.fr/
Union for International Cancer Control (UICC)	https://www.uicc.org/
International Association of Oncology (IAO)	https://iaoncology.org/about.php
International Society of Nurses in Cancer Care	https://www.isncc.org/
International Society of Geriatric Oncology	https://www.siog.org/
International Psycho-Oncology Society	https://www.ipos-society.org/

Source	Location
European Society for Medical Oncology	https://www.esmo.org/
European Cancer Organisation (ECCO)	https://www.ecco-org.eu/
The Organisation of European Cancer Institutes (OECI)	www.oeci.eu
European School of Oncology	www.eso.net
European Organisation for Research and Treatment of Cancer	www.eortc.org
The European Oncology Nursing Society (EONS)	www.cancernurse.eu
European Association of Urology (EAU)	www.uroweb.org
European Society of Breast Cancer	www.eusoma.org
Nordic Cancer Union	http://www.ncu.nu/Default.aspx?ID=23
Clinical Oncology Society of Australia	https://www.cosa.org.au/
Cancer Council	https://www.cancer.org.au/
Cancer Australia	https://canceraustralia.gov.au/
Belgian Cancer Registry	https://kankerregister.org/Home_en
The Belgium Society of Medical Oncology (BSMO)	https://www.bsmo.be/
Cyprus Anti-Cancer Society	https://www.anticancersociety.org.cy/en/page/home
Czech National Cancer Control Programme	https://www.onconet.cz/index-en.php
Danish Cancer Society	https://www.cancer.dk/international/
Dansk Selskab for Klinisk Onkologi/ Dansish Society for Clinical Oncology	https://dsko.org/
Cancer Society of Finland	https://www.cancersociety.fi/
Fondation de France/ Foundation of France	https://www.fondationdefrance.org/en/cancer
Institut Curie/ Curie Institute (France)	https://institut-curie.org/
Institut National Du Cancer/ National cancer institute (France)	https://www.e-cancer.fr/
Société Francaise du Cancer / French Ccancer Society	https://sfc.asso.fr/
Société Francaise de Radiothérapie Oncologique / French Society of Radiation Oncology	https://www.sfro.org/
Deutsches Krebsforschungszentrum - Stiftung des öffentlichen Rechts/ German Cancer Research Center - Foundation under Public Law	https://www.dkfz.de/en/index.html
Deutsches Krebsforschungszentrum- Tumorerkrankungen (NCT) Heidelberg / National Centre for Tumour Diseases Heidelberg	https://www.nct-heidelberg.de/en/the-nct/supporting-institutions/german-cancer-research-center-dkfz.html
Deutsche Krebsgesellschaft/ German Cancer Society	https://www.krebsgesellschaft.de/german-cancer-society.html
Cancer Society (Greece)	http://www.cancer-society.gr/
Hellenic Society of Medical oncology	https://www.hesmo.gr/en/
Hellenic Cancer Society	https://cancerhellas.org/
Krabbameinsfelagid (Iceland)	https://www.krabb.is/
Irish Cancer Society	https://www.cancer.ie/
National Cancer Ireland	https://www.ncri.ie/data
Associazione Italiana Malati di Cancrio / Italian Association of Cancer	https://www.aimac.it/

Source	Location
Patients	
Istitudo di Ricovero e Cura a Carattere Scientifico (IRCCS) / Scientific Hospitalization and Care institute	https://research.fpoircc.it/
Institut national du cancer / National Cancer Institute (Luxembourg)	http://institutnationalducancer.lu/
Fondation Cancer / Cancer Foundation (Luxembourg)	http://www.cancer.lu/
Centre Scientifique de Monaco / Monaco Scientific Centre	https://www.centrescientifique.mc/en/article/medical-biology/cancer
Netherlands Cancer Institute	https://www.nki.nl/
Dutch Cancer Society	https://www.kwf.nl/en/english
Kreftregistry / Cancer Registry of Norway	https://www.kreftregisteret.no/en/
Ligo Portuguesa Contra o Cancro / Portuguese Cancer League	https://www.ligacontracancro.pt/
Onkološki Inštitut Ljubljana / Institute of Oncology Ljubljana (Slovenia)	https://www.onko-i.si/
Zveza slovenskih društev za boj proti raku / Association of Slovenia Cancer Societies	http://www.protiraku.si/
Asociación Española Contra el Cáncer / Spanish Association Against Cancer	https://www.aecc.es/es
Institut Catalan d'Oncologia / Catalan Institute of Oncology	http://www.iconcologia.net/
Sociedad Española de Enfermería Oncológica / Spanish Oncology Nursing Society	https://seeo.org/
Cancerfonden / Cancer Foundation (Sweden)	https://www.cancerfonden.se/
Sjuksköterskor i cancervård / Nurses in Cancer Care	https://www.swenurse.se/Sektioner-och-Natverk/Sjukskoterskoricancervard/
Krebsliga / SwissCancer League	https://www.krebsliga.ch/
NICER - Nationales Institut für Krebsepidemiologie und -registrierung / Foundation National Institute for Cancer Epidemiology and Registration (Switzerland)	https://www.nicer.org/
Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung / Swiss Group for Clinical Cancer Research	https://www.sakk.ch/en
National Cancer Institute (USA)	https://www.cancer.gov/
National Comprehensive Cancer Network (USA)	https://www.nccn.org/
American Society of Clinical Oncology (ASCO)	https://www.asco.org/
Cancer Research UK	https://www.cancerresearchuk.org/
Royal College of Radiologists (UK)	https://www.rcr.ac.uk/

12.2 Search results

Search result summaries

Table 12-3 Summary of biomedical database search results

Source	Results
PubMed	2,402
Embase	6,368
The Cochrane Library (inc. CENTRAL)	45
CINAHL	418
York CRD	61
Econlit	8
PsychInfo	21
ETHMED	8
Total	**9,331**

Table 12-4 Summary of grey literature search results

Source	Results
Clinical practice guideline websites	19
HTA websites	60
Specialty websites	19
Total	**98**

Search results for individual bibliographic databases

Table 12-5 PubMed (MEDLINE) search string [22 May 2020]

No.	Query	Results
1	Osteoporosis, postmenopausal [mh]	12,985
2	Osteoporosis [mh]	55,073
3	Osteoporotic fracture [mh]	5,388
4	Menopause [mh]	5,423
5	Osteodensitomet*[tiab]	282
6	Osteoporo* [tiab]	76,589
7	Postmenopaus*[tiab]	54,256
8	Menopaus*[tiab]	48,859
9	Spinal fractures [mh]	14,706

10	Rib fractures [mh]	3,041
11	Shoulder fractures [mh]	3,402
12	Fractures, bone [mh: noexp]	63,665
13	Ankle fractures [mh]	1,426
14	Hip fractures [mh]	23,592
15	Fractur* [tiab]	258,095
16	Break [tiab]	46,271
17	Breaks [tiab]	43,081
18	Bone density [mh]	52,676
19	(bone density)	94,945
20	Calcium [mh:noexp]	266,154
21	Vitamin D deficiency [mh]	27,482
22	Calcium [tiab]	375,197
23	Vitamin D [tiab]	62,378
24	Vit D [tiab]	434
25	(Bone loss)	151,569
26	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25**	**1,110,006**
27	Chemotherapy, adjuvant [mh]	40,154
28	Radiotherapy, adjuvant [mh]	22,172
29	Adjuvant treatment [tiab]	13,464
30	Adjuvant therapy [tiab]	24,027
31	**27 OR 28 OR 29 OR 30**	**80,626**
32	Aromatase inhibitors [mh]	6,137
33	Aromatase inhibit* [tiab]	7,580
34	**32 OR 33**	9, 350
35	Breast neoplasms [mh]	289,059
36	Breast cancer lymphedema [mh]	173
37	Breast cancer [tiab]	267,917
38	Breast cancers [tiab]	22,793
39	Breast neoplasms [tiab]	9,305
40	Breast neoplasm [tiab]	787
41	**35 OR 36 OR 37 OR 38 OR 39 OR 40**	**367,409**
42	**31 AND 34 AND 41**	**1,538**
43	Ablation therapy [tw]	2,312
44	Hormon* therapy [tiab]	159,711
45	Hormon* treatment [tw]	303,438
46	Androgen suppress* [tw]	806

47	**43 OR 44 OR 45 OR 46**	**305,710**
48	Prostate neoplasms [mh]	126,497
49	Prostat* neoplasms [tiab]	6,409
50	Prostat* neoplasm [tiab]	2,010
51	Prostat* cancer [tiab]	140,660
52	Prostat* cancers [tiab]	22,117
53	**48 OR 49 OR 50 OR 51 OR 52**	**22,188**
54	**47 AND 53**	**10,393**
55	**26 OR 42 OR 54**	**1, 299,300**
56	Denosumab [mh]	1,574
57	Denosumab [tiab]	2,738
58	Prolia [tw]	44
59	**56 OR 57 OR 58**	**2,972**
60	RANK [tw]	105,509
61	Ligand [tw]	290,412
62	**60 AND 61**	**9,490**
63	Rank Ligand [mh]	7,346
64	RANKL [tw]	9,825
65	**63 OR 64**	13,146
66	Inhibit* [tw]	268,6491
67	**(62 OR 65) AND 66**	**6,519**
68	**59 OR 67**	**8,920**
69	**55 AND 68**	**5,244**
		Filtered
70	**69 AND systematic review filter**	**253**
71	**69 AND cost-effectiveness filter**	**229**
72	**69 AND social considerations search string**	**74**
73	**69 AND ethical considerations search string**	**46**
74	**69 AND legal considerations search string**	**1,555**
75	**69 AND organisational considerations search string**	**245**

Table 12-6 Embase (OVID) search string [22 May 2020]

No.	Query	Results
1	Exp Osteoporosis, postmenopausal/	14,078
2	Exp Osteoporosis /	127,093
3	Exp Osteoporotic fracture /	17,716
4	Exp Menopause /	45,322
5	Osteodensitomet.ti,ab,kw.	0
6	Osteoporo*.ti,ab,kw.	120,231
7	Postmenopaus*.ti,ab,kw.	77,880
8	Menopaus*.ti,ab,kw.	75,338
9	Exp Spinal fractures/	27,531
10	Exp Rib fractures/	8,016
11	Exp Shoulder fractures/	2,602
12	Fractures, bone/	28,637
13	Exp Ankle fractures/	6,392
14	Exp Hip fractures/	37,471
15	Fractur*.ti,ab,kw.	301,486
16	Break.ti,ab,kw.	58,734
17	Breaks.ti,ab,kw.	52,300
18	Exp Bone density/	92,250
19	bone density.ti,ab,kw.	23,269
20	Calcium/	276,748
21	Exp Vitamin D deficiency/	29,429
22	Calcium.ti,ab,kw	471,066
23	Vitamin D.ti,ab,kw	92,205
24	Vit D.ti,ab,kw	1,920
25	Bone loss.ti,ab,kw	37,728
26	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25**	**1,260,679**
27	Exp Chemotherapy, adjuvant/	54,347
28	Exp Radiotherapy, adjuvant/	12,464
29	Adjuvant treatment.ti,ab,kw	22,782
30	Adjuvant therapy.ti,ab,kw	38,382
31	**27 OR 28 OR 29 OR 30**	**106,093**
32	Exp Aromatase inhibitors/	31,668
33	Aromatase inhibit*.ti,ab,kw	12,426
34	**32 OR 33**	33,006
35	Exp Breast neoplasms/	527,145

36	Exp Breast cancer lymphedema/	437
37	Breast cancer.ti,ab,kw	396,998
38	Breast cancers.ti,ab,kw	396,998
39	Breast neoplasms.ti,ab,kw	9,348
40	Breast neoplasm.ti,ab,kw	1,878
41	**35 OR 36 OR 37 OR 38 OR 39 OR 40**	**575,990**
42	**31 AND 34 AND 41**	**19**
43	Ablation therapy.ti,ab,kw	3,820
44	Hormon* therapy.ti,ab,kw	34,904
45	Hormon* treatment.ti,ab,kw	13,732
46	Androgen suppress*.ti,ab,kw	1,185
47	**43 OR 44 OR 45 OR 46**	**51,405**
48	Exp Prostate cancer/	214,969
49	Prostat* neoplasms.ti,ab,kw	7,747
50	Prostat* neoplasm.ti,ab,kw	942
51	Prostat* cancer.ti,ab,kw	183,196
52	Prostat* cancers.ti,ab,kw	9,251
53	**48 OR 49 OR 50 OR 51 OR 52**	**246,578**
54	**47 AND 53**	**10,594**
55	**26 OR 42 OR 54**	**1,270,699**
56	Exp Denosumab /	8,583
57	Denosumab.ti,ab,kw	5372
58	Prolia.ti,ab,kw	104
59	**56 OR 57 OR 58**	**8,989**
60	RANK.ti,ab,kw	172,125
61	Ligand.ti,ab,kw	323,904
62	**60 AND 61**	**4,863**
63	Exp Rank Ligand/	18,482
64	RANKL.ti,ab,kw	15,197
65	**63 OR 64**	**20,732**
66	Inhibit*.ti,ab,kw	2,905,819
67	**(62 OR 65) AND 66**	**9,809**
68	**59 OR 67**	**17,696**
69	**55 AND 68**	**9,944**
Filtered		
70	**69 AND systematic review filter**	**644**
71	**69 AND cost-effectiveness filter**	**729**
72	**69 AND social considerations search string**	**549**

73	**69 AND ethical considerations search string**	**546**
74	**69 AND legal considerations search string**	**2,268**
75	**69 AND organisational considerations search string**	**1,632**

Table 12-7 Cochrane Library [28 May 2020]

No.	Query	Results
1	Osteoporo*	11,769
2	Postmenopaus*	20,766
3	Menopaus*	13,141
4	Fractur*	22,229
5	Break	3,760
6	Breaks	1,563
7	bone density	12,244
8	Calcium	29,728
9	Vitamin D	15,750
10	Vit D	670
11	Bone loss	9,671
12	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11**	**9,5293**
13	Chemotherapy, adjuvant	15,923
14	Radiotherapy, adjuvant	6,780
15	Adjuvant treatment	21,193
16	Adjuvant therapy	2,3059
17	**#13 OR #14 OR #15 OR #16**	**28,356**
18	Aromatase inhibitors	1,426
19	Aromatase inhibit*	2,258
20	**#18 OR #19**	**2,258**
21	Breast cancer	36,003
22	Breast cancers	2,493
23	Breast neoplasms	14,175
24	Breast neoplasm	4,928
25	**#21 OR #22 OR #23 OR #24**	**36,610**
26	**#17 AND #20 AND #25**	**806**
27	Ablation therapy	4,235
28	Hormon* therapy	31,776
29	Hormon* treatment	32,049
30	Androgen suppress*	750
31	**#27 OR #28 OR #29 OR #30**	**44,591**

32	Prostat* neoplasms	7,224
33	Prostat* neoplasm	2,388
34	Prostat* cancer	14,763
35	Prostat* cancers	1,347
36	**#32 OR #33 OR #34 OR #35**	**15,229**
37	**#31 AND #36**	**100,044**
38	Denosumab	935
39	Prolia	49
40	**#38 OR #39**	**938**
41	RANK	17,326
42	Ligand	3,086
43	**#41 AND #42**	283
44	Rank Ligand	283
45	RANKL	468
46	**#44 OR #45**	**608**
47	Inhibit*	123,686
48	**(#44 OR #45) AND #47**	**262**
49	**#43 AND #47**	**141**
50	**#40 OR #48 OR #49**	**1,044**
51	**#12 OR #26 OR #37**	**98,340**
52	**#50 AND #51**	**828**
Filtered		
53	**#52 in Cochrane Reviews**	**45**
54	**#52 in Trials**	**824**

Table 12-8 CINAHL search string [12 May 2020]

No.	Query	Results
1	MH “Osteoporosis, postmenopausal+”	4,243
2	MH “Osteoporosis+”	24,552
3	MH “Menopause”	8,846
4	TX “Osteodensitomet*”	49
5	TX “Osteoporo*”	47,893
6	TX “Postmenopaus*”	29,822
7	TX “Menopaus*”	32,397
8	MH “Spinal fractures+”	5,873
9	MH “Rib fractures+”	860
10	MH “Shoulder fractures+”	1,428

11	MH “Ankle fractures”	1,851
12	MH “Hip fractures+”	10,660
13	TX “Fractur*”	115,007
14	TX “Break”	53,596
15	TX “Breaks”	23,919
16	MH “Bone density+”	18,901
17	TX “bone density”	23,519
18	MH “Calcium+”	15,375
19	MH “Vitamin D deficiency+”	8,829
20	TX “Calcium”	71,557
21	TX “Vitamin D”	33,112
22	TX “Vit D”	227
23	TX “Bone loss”	11,681
24	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23**	**330,651**
25	MH “Chemotherapy, adjuvant+”	11,826
26	MH “Radiotherapy, adjuvant+”	5,175
27	TX “Adjuvant treatment”	5,154
28	TX “Adjuvant therapy”	8,412
29	**25 OR 26 OR 27 OR 28**	**24,592**
30	MH “Aromatase inhibitors”	1,981
31	TX “Aromatase inhibit*”	4,177
32	**30 OR 31**	4,177
33	MH “Breast neoplasms”	85,721
34	TX “Breast cancer”	107,517
35	TX “Breast cancers”	7,363
36	TX “Breast neoplasms”	86,318
37	TX “Breast neoplasm”	219
38	**33 OR 34 OR 35 OR 36 OR 37**	**132,950**
39	**29 AND 32 AND 38**	**1,322**
40	TX “Ablation therapy”	1,215
41	TX “Hormon* therapy”	13,194
42	TX “Hormon* treatment”	2,435
43	TX “Androgen suppress*”	358
44	**40 OR 41 OR 43**	**16,245**
45	TX “Prostat* neoplasms”	31,219
46	TX “Prostat* neoplasm”	37
47	TX “Prostat* cancer”	42,508

48	TX “Prostat* cancers”	2,140
49	**45 OR 46 OR 47 OR 48**	**50,832**
50	**44 AND 49**	**3,090**
51	**21 OR 39 OR 50**	333,087
52	TX “Denosumab”	1,582
53	TX “Prolia”	131
54	**52 OR 53**	**1,601**
55	TX “RANK”	1,395,818
56	TX “Ligand”	12,843
57	**55 AND 56**	**1,123**
58	TX “Rank Ligand”	301
59	TX “RANKL”	1,998
60	**58 OR 59**	**2,113**
61	TX “Inhibit*”	298,395
62	**(57 OR 60) AND 61**	**1,162**
63	**54 OR 62**	**2,474**
64	**51 AND 63**	**1,839**
Filtered		
65	**64 AND systematic review filter**	**339**
67	**64 AND cost-effectiveness filter**	**79**

Table 12-9 Search Strategy – York CRD (including DARE, NHS EED, HTA) [Updated: 1 October 2020]

Number	Query	Results
1	Denosumab	61

Table 12-10 EconLit (EBSCO) search string [28 May 2020]

No.	Query	Results
1	TX “Osteoporo*”	374
2	TX “Postmenopaus*”	103
3	TX “Menopaus*”	428
4	TX “Fractur*”	3,953
5	TX “Break”	51,423
6	TX “Breaks”	26,049
7	TX “bone density”	44

8	TX “Calcium”	787
9	TX “Vitamin D”	202
10	TX “Vit D”	23
11	TX “Bone loss”	15
12	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11**	71,743
13	TX “Chemotherapy”	595
14	TX “Radiotherapy”	215
15	TX “Adjuvant treatment”	28
16	TX “Adjuvant therapy”	36
17	**13 OR 14 OR 15 OR 16**	732
18	TX “Aromatase inhibitors”	9
19	TX “Aromatase inhibit*”	11
20	**18 OR 19**	11
21	TX “Breast neoplasms”	3
22	TX “Breast cancer”	1,573
23	TX “Breast cancers”	61
24	TX “Breast neoplasms”	3
25	**21 OR 22 OR 23 OR 24**	1,584
26	**17 AND 20 AND 25**	**9**
27	TX “Ablation therapy”	0
28	TX “Hormon* therapy”	68
29	TX “Hormon* treatment”	30
30	TX “Androgen suppress*”	1
31	**27 OR 28 OR 29 OR 30**	**97**
32	TX “Prostat* neoplasm”	0
33	TX “Prostat* cancer”	435
34	TX “Prostat* cancers”	33
35	**32 OR 33 OR 34**	456
36	**31 AND 35**	18
37	**12 OR 26 OR 36**	**71,755**
38	TX “Denosumab”	**7**
39	TX “Prolia”	**0**
40	**38 OR 39**	7
41	TX “RANK”	48,735
42	TX “Ligand”	17
43	**41 AND 42**	4
44	TX “Rank Ligand”	2
45	TX “RANKL”	9

46	**44 OR 45**	10
47	TX "Inhibit*"	18,453
49	**(43 OR 46) AND 47**	4
50	**40 AND 49**	8

Table 12-11 PsycINFO (OVID) search string [27 May 2020]

No.	Query	Results
1	Exp Osteoporosis /	1,077
2	Exp Menopause /	3,746
3	Osteodensitomet.ti,ab.	0
4	Osteoporo*.ti,ab.	2,028
5	Postmenopaus*.ti,ab.	2,541
6	Menopaus*.ti,ab.	4,654
7	Fractures, bone/	0
8	Fractur*.ti,ab.	4,749
9	Break.ti,ab.	0
10	Breaks.ti,ab.	10,500
11	bone density.ti,ab.	4,079
12	Calcium/	352
13	Calcium.ti,ab.	3,601
14	Vitamin D.ti,ab.	13,777
15	Vit D.ti,ab.	1,884
16	Bone loss.ti,ab.	7
17	**Or/1-16**	264
18	Exp Chemotherapy/	41,692
19	Adjuvant treatment.ti,ab.	3,052
20	Adjuvant therapy.ti,ab.	369
21	**Or/18-20**	3,744
22	**Aromatase inhibit*.ti,ab.**	**276**
23	Exp Breast neoplasms/	3,808
24	Breast cancer.ti,ab.	11,774
25	Breast cancers.ti,ab.	173
26	Breast neoplasms.ti,ab.	**4**
27	Breast neoplasm.ti,ab.	4
28	**Or/23-27**	12,621
29	**21 AND 22 AND 28**	19

30	Ablation therapy.ti,ab.	8
31	Hormon* therapy.ti,ab.	**1,260**
32	Hormon* treatment.ti,ab.	751
33	Androgen suppress*.ti,ab.	12
34	**Or/30-33**	1,937
35	Exp Prostate cancer/	4,635
36	Prostat* neoplasms.ti,ab.	5
37	Prostat* neoplasm.ti,ab.	0
38	Prostat* cancer.ti,ab.	2,902
39	Prostat* cancers.ti,ab.	82
40	**Or/35-39**	7,093
41	**34 AND 40**	**91**
42	**17 OR 29 OR 41**	**41,782**
43	Denosumab.ti,ab.	16
44	Prolia.ti,ab.	0
45	**Or/43-44**	16
46	RANK.ti,ab.	19,475
47	Ligand.ti,ab.	**5,382**
48	**46 AND 47**	23
49	RANKL.ti,ab.	29
50	Inhibit*.ti,ab.	148,383
51	**(48 OR 49) AND 50**	18
52	**45 OR 51**	32
53	**42 AND 52**	**23**
54	**53 AND ethical considerations search string**	**1**
55	**53 AND legal considerations search string**	**3**
56	**53 AND social considerations search string**	**17**

Table 12-12 ETHMED search string [27 May 2020]

Auxiliary search strings	Results
Osteoporosis	6
Menopause	2
post-menopause AND denosumab	0
Denosumab	0
Prolia	0

12.3 Search strings and filters

The following methodological search filters (***Table 12-13*** and ***Table 12-14***) were developed by the *Canadian Agency for Drugs and Technologies in Health* (CADTH),[87] whereas the topical search strings (***Table 12-13*** to ***Table 12-15***) were developed by the HTA authors. These filters and search strings were combined with the population and intervention terms outlined in ***Table 12-5.***

Methodological Search Filters

Table 12-13 Systematic review and HTA filter (PubMed (MEDLINE))

No.	Query
1	Systematic[sb]
2	Meta-analysis[pt]
3	Meta-analysis as topic[mh]
4	Meta-analysis[mh]
5	Meta analy*[tw]
6	Integrative review*[tiab]
7	Integrative overview*[tiab]
8	Research integration*[tiab]
9	Research overview*[tiab]
10	Collaborative review*[tiab]
11	Collaborative overview*[tiab]
12	Systematic review*[tiab]
13	Technology assessment*[tiab]
14	Technology overview*[tiab]
15	Technology assessment, biomedical [mh]
16	Hta[tiab]
17	Htas[tiab]
18	Comparative efficacy[tiab]
19	Comparative effectiveness[tiab]
20	Outcomes research[tiab]
21	Indirect comparison*[tiab]
22	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21**
23	Indirect treatment[tiab]
24	Mixed-treatment[tiab]
25	**23 OR 24**
26	Comparison*[tiab]
27	**25 AND 26**
28	Embase*[tiab]
29	Cinahl*[tiab]
30	Systematic overview*[tiab]
31	Methodological overview*[tiab]

32	Methodologic overview*[tiab]
33	Methodological review*[tiab]
34	Methodologic review*[tiab]
35	Quantitative review*[tiab]
36	Quantitative overview*[tiab]
37	Quantitative synthes*[tiab]
38	Pooled analy*[tiab]
39	Cochrane[tiab]
40	Medline[tiab]
41	Pubmed[tiab]
42	Medlars[tiab]
43	Handsearch*[tiab]
44	Hand search*[tiab]
45	Meta-regression*[tiab]
46	Metaregression*[tiab]
47	Data synthes*[tiab]
48	Data extraction[tiab]
49	Data abstraction*[tiab]
50	Mantel haenszel[tiab]
51	Peto[tiab]
52	Der-simonian[tiab]
53	Dersimonian[tiab]
54	Fixed effect*[tiab]
55	"cochrane database syst rev"[journal]
56	"health technology assessment winchester, england"[journal]
57	"evid rep technol assess (full rep)"[journal]
58	"evid rep technol assess (summ)"[journal]
59	"int j technol assess health care"[journal]
60	"gms health technol assess"[journal]
61	"health technol assess (rockv)"[journal]
62	"health technol assess rep"[journal]
63	**28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62**
64	**22 OR 27 OR 63**

Source
CADTH[179]

Table 12-14 Cost-effectiveness filter (PubMed (MEDLINE))

No.	Query
1	Economics[mesh:noexp]
2	Costs and cost analysis [mh]
3	Economics, nursing[mh]
4	Economics, medical[mh]
5	Economics, pharmaceutical[mh]

6	Economics, hospital[mh]
7	Economics, dental[mh]
8	Fees and charges[mh]
9	Budgets[mh]
10	Budget*[tiab]
11	Economic*[tiab]
12	Cost[tiab]
13	Costs[tiab]
14	Costly[tiab]
15	Costing[tiab]
16	Price[tiab]
17	Prices[tiab]
18	Pricing[tiab]
19	Pharmacoeconomic*[tiab]
20	Pharmaco-economic*[tiab]
21	Expenditure[tiab]
22	Expenditures[tiab]
23	Expense[tiab]
24	Expenses[tiab]
25	Financial[tiab]
26	Finance[tiab]
27	Finances[tiab]
28	Financed[tiab]
29	Value for money[tiab]
30	Monetary value*[tiab]
31	Models, economic[mh]
32	Economic model*[tiab]
33	Markov chains[mh]
34	Markov[tiab]
35	Monte carlo method[mh]
36	Monte carlo[tiab]
37	Decision theory[mh]
38	Decision tree*[tiab]
39	Decision analy*[tiab]
40	Decision model*[tiab]
41	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40**

Source

CADTH[179]

Topical Search Strings

Table 12-15 Search string for legal considerations (PubMed (MEDLINE))

No.	Query
1	Personal autonomy [mh]
2	Human rights [mh]
3	Right*[tiab]
4	(free will)
5	(self determination)
78	Parental consent [mh]
9	Third-party consent [mh]
10	Presumed consent [mh]
11	Informed consent by minors [mh]
12	Consent [tiab]
13	Privacy [tw]
14	Confidentiality [mh]
15	Confident*[tiab]
16	Personaly identifiable information [mh]
17	Health record, personal [mh]
18	(personal information)
19	Jurisprudence [mh]
20	Law enforcement [mh]
21	Law[tiab]
22	Laws[tiab]
23	Legislation, drug [mh]
24	Legislation, pharmacy [mh]
25	Legislation, food [mh]
26	Legislation as topic [mh]
27	Legislat*[tiab]
28	Civil rights [mh]
29	Authorit*[tiab]
30	Legal.case [pt]
31	Legal guardians [mh]
32	Legal [tiab]
33	Liability, legal [mh]
34	Legal services [mh]
35	Access to information [mh]
36	Social justice [mh]
37	Health equity [mh]
38	Human rights abuses [mh]
39	Patient rights [mh]
40	Rights to human [mh]
41	Ownership [mh]
42	Intellectual property [mh]

43	lp [tiab]
44	Licensure [mh]
45	Licens*[tiab]
46	Liability, legal [mh]
47	Liability [tiab]
48	Legislat* [tiab]
49	Legislation as topic [mh]
50	Medical device legislation [mh]
51	Legislation, nursing [mh]
52	Legislation, medical [mh]
53	Legislation, hospital [mh]
54	Legislation, food [mh]
55	Legislation, drug [mh]
56	Conflict of interest [mh]
57	Guarant* [tiab]
58	Regulat* [tiab]
59	Acquisition
60	Coi [tiab]
61	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 PR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60**

Source
Created by authors

Table 12-16 Search string for organisational issues (PubMed (MEDLINE)) [3 March 2020]

No.	Query
1	Information storage and retrieval [mh]
2	(information management)
3	Health information systems [mh]
4	Health information management [mh]
5	Health information exchange [mh]
6	Information literacy [mh]
7	Health equity [mh]
8	(work process)
9	(work flow)
10	Education [mh]
11	Education, professional, retraining [mh]
12	Education, public health professional [mh]
13	Train* [tiab]
14	Health information interoperability[mh]
15	Communication [mh]
16	Health communication [mh]
18	Quality assurance, health care [mh]
19	Implementation science [mh]

20	Organisation culture [mh]
21	(human skills)
22	Sustainabil* [tiab]
23	(system structure)
24	Accep*[tiab]
25	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24**

Source
Created by authors

Table 12-17 Search string for ethical considerations (PubMed (MEDLINE)) [3 March 2020]

No.	Query
1	Ethics[mh]
2	Ethic*[tiab]
3	Ethical theory [mh]
4	Bioethics[mh]
5	Bioethic*[tiab]
6	Morals[mh]
7	Moral*[tiab]
8	Principle-based ethics[mh]
9	Principl*[tiab]
10	Patient rights [mh]
11	Patient autonomy[tiab]
12	Personal autonomy [mh]
13	Autonom*[tiab]
14	Social justice [mh]
15	Patient rights[mh]
16	Ethical issues [tiab]
17	Normative [tiab]
18	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17**

Source
Created by authors

Table 12-18 Search string for social considerations (PubMed (MEDLINE)) [3 March 2020]

No.	Query
1	Patient experien* [tiab]
2	Quality of life [mh]
3	Social aspects of [tiab]
4	Medical decision-making process [mh]
5	Patient education as topic [mh]
6	Patient educati* [tiab]
7	Patient attitude* [tiab]
8	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7**

Source
Created by authors

13 Appendix B: Effectiveness/efficacy and safety study extraction

Table 13-1 Outcomes reported in RCTs comparing denosumab (Prolia®) to placebo

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Men with increased fracture risk											
ADAMO trial											
Langdahl, 2015 [108] Belgium, Canada Denmark, France, Poland, Sweden, USA	Pros, randomised, double-blind (some side studies had OL periods)	Men with osteoporosis and increased risk of fracture (n=242)	✓ 24 mo	x	✓ 6, 12, 18, 24 mo (lumbar spine, total hip, femoral neck, trochanter, distal 1/3 radius)	✓ 6, 12, 18, 24 mo (sCTX)	x	✓ 24 mo	x	✓ 24 mo	x
Orwoll, 2012 [115] Belgium, Canada Denmark, France, Poland, Sweden, USA	Pros, randomised (1:1), double-blind	Men with osteoporosis and increased risk of fracture (n=242)	✓ 12 mo	x	✓ 6, 12 mo (lumbar spine, total hip, femoral neck, trochanter, distal 1/3 radius)	✓ 6, 12 mo (sCTX)	x	✓ 12 mo	x	✓ 12 mo	x
Women with breast cancer on AAIT											
Independent studies											

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Ellis, 2008 [104] Canada, USA	Pros, randomised (1:1), double-blind	Women with breast cancer on AAIT (n=252)	✓ 24 mo	x	✓ 1, 3, 6, 12, 24, (lumbar spine, total hip) 12, 24 mo (1/3 radius)	✓ 1, 6, 12, 24 mo (sCTX, sP1PN)	x	✓ 24 mo	x	✓ 24 mo	✓ 24 mo
Gnant, 2015 [105] Austria	Pros, randomised, double-blind	Women with breast cancer on AAIT (n=3,425)	✓ 72 mo (time to first clinical fracture)	x	✓ 12, 24, 36 mo (lumbar spine, total hip, femoral neck)	x	✓ every 6 months for 75 months	✓ 72 mo	x	✓ 72 mo	✓ 72 mo
Men with prostate cancer on HAT											
Same unnamed trial											
Egerdie, 2012[103] Canada, Czech Republic, Finland, USA	Pros, randomised, double-blind	Men with prostate cancer on HAT (n=1,468)	x	x	✓ 1, 2, 3, 6, 12, 24, 36 mo (lumbar spine, femoral neck, total hip, distal 1/3 radius)	x	x	n/a[a]	n/a[a]	n/a[a]	x
Smith, 2009[123] Canada, Czech Republic, Finland, USA	Pros, randomised, double-blind	Men with prostate cancer on HAT (n=156)	✓ 12, 24, 36 mo	x	✓ 1, 3, 6, 12, 24, 36 mo (lumbar spine, total hip, femoral neck, distal 1/3 radius)	✓ 36 mo (sNTX, TRAP-5b-percentage change and p value only)	✓ 36 mo	✓ 36 mo	x	✓ 36 mo	✓ 36 mo
Postmenopausal women											
FRAME extension											

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Lewiecki, 2019 [130] USA	Pros, single-arm, OL	Postmenopausal women (n=6,045)	Data not usable[a]					n/a	✓	x (not distinct from main study)	x
FREEDOM trial											
Boonen, 2011 [100] Argentina, Belgium, Canada, USA, Spain, Sweden, Switzerland	Pros, randomised, double-blind	Postmenopausal women (n=7,808)	✓ 6, 12, 18, 24, 30, 36	x	x	x	✓ 6, 12, 18, 24, 30, 36 mo	✓ 36 mo	x	✓ 36 mo	x
Cummings, 2009[101] Argentina, Czech Republic, Denmark, France, Italy, New Zealand, UK, USA	Pros, randomised, double-blind	Postmenopausal women (n=7,808)	✓ 12, 24, 36 mo	x	✓ 6, 12, 18, 24, 30, 36 mo (lumbar spine, total hip)	✓ 6, 12, 18, 24, 30, 36 mo (sCTX, sP1NP)	✓ 36 mo	✓ 36 mo	x	✓ 36 mo	x

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Eastell, 2011[102] Austria, Czech Republic, Denmark, France, New Zealand, Switzerland, UK, USA	Pros, randomised, blinding NR	Postmenopausal women (n=160)	x	x	x	✓ 1, 6, 12, 24, 36 mo (sCTX, sP1NP, sTRAP-5b, sB-ALP)	x	x	x	x	x
McClung, 2012[110] Belgium, Denmark, France, Italy, Netherlands, Norway, Sweden, Switzerland, UK, USA	Pros, randomised, double-blind	Postmenopausal women (n=7,808)	✓ 36 mo (forest plot)	x	✓ 36 mo (femoral neck)	x	x	x	x	x	X
Palacios, 2015[116] Austria, Canada, Italy, Spain, Switzerland, USA	Pros, randomised, double-blind	Postmenopausal women (n=7,808)	✓ 36 mo	x	x	x	✓ 36 mo	✓ 36 mo	x	✓ 36 mo	x

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Simon, 2013[122] Argentina, Australia, Austria, Brazil. Canada, Italy, Poland, Sweden, USA	Pros, randomised, double-blind	Postmenopausal women (7,808)	✓ 36 mo	x	✓ 12, 24, 36 mo (total radius, distal 1/3 radius, ultradistal radius)	x	✓ 12, 24, 36 mo (derived from Kaplan-Meir curves)	x	x	x	x
Watts, 2012 [124] Canada, France, USA	Pros, randomised, double-blind	Postmenopausal women (n=7,808)	x	x	x	x	x	✓ 36 mo	x	✓ 36 mo	x
FREEDOM extension											
Adachi, 2017[126] Canada, Germany, Netherlands, Switzerland, USA	Pros, single-arm, OL	Postmenopausal women (n=3,258)	Data not usable[a]					n/a	✓ 5 years	✓ 5 years	x
Bone, 2013[127] Austria, Belgium, Brazil, Canada, France, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, USA	Pros, single-arm, OL	Postmenopausal women (n=4,550)	Data not usable[a]					n/a	✓ 7 years	✓ 7 years	✓ 7 years

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Bone, 2017[128] Austria, Belgium, Canada, France, Italy, Netherlands, Poland, Spain, Switzerland, USA	Pros, single-arm, OL	Postmenopausal women (n=4,550)	Data not usable[a]					n/a	✓ 10 years	✓ 10 years	✓ 10 years
Brown, 2013[129] Canada, Denmark, France, New Zealand, Sweden, USA	Pros, single-arm, OL	Postmenopausal women (n=797)	Data not usable[a]					n/a	✓ 7 mo	✓ 7 mo	X
Cummings, 2018[85] Denmark, Estonia, France, New Zealand, Sweden, Switzerland, UK, USA	Pros, OL	Postmenopausal women (n=4,550)	Data not usable[a]					n/a	✓ 7 mo	✓ 7 mo	✓ 7 mo

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Papapoulos, 2012[132] Argentina, Austria, Belgium, Brazil, Canada, France, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, USA	Pros, OL	Postmenopausal women (n=4,550)	Data not usable[a]					n/a	✓ 2 years	✓ 2 years	✓ 2 years
Popp, 2018[133] Switzerland	Pros, OL	Postmenopausal women (n=12)	Data not usable[a]					n/a	✓ 10 years	x	x
Watts, 2019[134] Australia, Netherlands, USA	Pros, OL	Postmenopausal women (n=4,550)	Data not usable[a]					n/a	✓ 10 years	x	x
Zanchetta, 2018[135] Argentina	Pros, OL	Postmenopausal women (n=56)	Data not usable[a]					n/a	✓ 17 mo	✓ 17 mo	X
NCT00043186 trial											

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Bone, 2008Lewiecki, 2007[109] USA	Pros, randomised, double-blind	Postmenopausal women (n=412)	x	x	✓ 1, 3, 6, 12, 18, 24 mo (lumbar spine, total hip) 6, 12, 18, 24 mo (distal 1/3 radius, total body)	✓ 1, 3, 6, 12, 15, 18, 21, 24 mo (sCTX, uNTX, B-ALP)	x	✓ 24 mo	x	✓ 24 mo	x
Lewiecki, 2007McClung, 2006[111] USA	Pros, randomised, double-blind	Postmenopausal women (n=412)	✓ 12 mo	x	✓ 1, 3, 6, 12 mo (lumbar spine, total hip, 6, 12 mo (distal 1/3 radius, total body)	✓ 3d, 1, 2, 3, 4, 5, 6, 6-3d, 7, 8, 9, 10, 11, 12 mo (sCTX) 1, 3, 6, 9, 12mo (sB-ALP)	x	✓ 12 mo	x	✓ 12 mo	x
Miller, 2008[112] USA	Pros, randomised, treatment blinded (one cohort OL)	Postmenopausal women (n=412)	✓ 48 mo	x	✓6, 12, 18, 24, 36, 48 mo (lumbar spine, total hip, distal 1/3 radius)	✓ 6, 12, 18, 24, 30, 36, 42, 48 mo (sCTX, B-ALP)	x	✓ 48 mo	✓36, 48 mo	✓ 48 mo	x
NCT00091793 trial											
Bone, 2008[99] Canada, USA	Pros, randomised (1:1), double-blind	Postmenopausal women (n=332)	✓ 24 mo	x	✓ 1, 6, 12 24 mo (lumbar spine, ✓ 12, 24 mo (distal 1/3 radius, total hip)	✓ 1, 6, 10, 12, 14, 17 24 mo (sCTX, TRAP-5b, sP1NP)	x	✓ 24 mo	x	✓ 24 mo	x

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Bone, 2011[53] (extension of Bone, 2008) Canada, USA	Pros, randomised (1:1), double-blind	Postmenopausal women (n=256)	✓ 24 mo	x	x	✓ 3, 6, 12, 18, 24 mo (sCTX, sP1NP)	x	✓ 24 mo	✓ 3, 6, 12, 18, 24 mo	✓ 24 mo	x
Independent studies											
Beck, 2008[98] Germany, USA	Pros (post hoc analysis), randomised (1:1:1), blind for denosumab and placebo	Postmenopausal women (n=116)	x	x	✓ 12, 24 mo (femoral neck, narrow neck, intertrochanter and femoral shaft)	x	x	x	x	x	x
Miller, 2011[131] USA	Pros, single-arm extension, OL	Postmenopausal women (n=200)	Data not usable [a]					x	✓ 24 mo	✓ 24 mo	x
Nakamura, 2012[114] Japan	Pros, randomised, double-blind	Postmenopausal women (n=226)	✓ 12 mo (no new fractures reported)	x	✓ 1, 3, 6, 12 mo (lumbar spine, total hip, distal 1/3 radius,	✓ 1, 3, 6, 7, 9, 12 mo (sCTX, sNTX, sB-ALP)	x	✓ 12 mo	x	x	x

Abbreviations

AAIT: adjuvant aromatase inhibitors therapy; **AE:** adverse event; **BMD:** bone mineral density; **BTM:** bone turnover marker; **DIRECT:** denosumab fracture intervention randomised placebo controlled trial; **FRAME:** fracture study in menopausal women with osteoporosis; **FREEDOM:** fracture reduction evaluation of denosumab in osteoporosis every 6 months; **HAT:** hormone ablation therapy; **HRQoL:** health-related quality of life; **NR:** not reported; **OL**: open label; **Pros:** prospective; **Retro:** retrospective; **sB-ALP:** serum bone-specific alkaline phosphatase, **sCTX:** serum C-terminal telopeptide of type 1 collagen; **sNTX:** serum N-terminal telopeptide of type 1 collagen; **sP1NP:** Serum procollagen type 1 propeptide; **TRAP:** tartare-resistant acid phosphatase; **uNTX:** urine N-terminal telopeptide of type 1 collagen.

Explanatory notes

[a] Effectiveness data for these studies is not usable as the trials became single-arm during the extension study.

n/a: Not applicable as the detailed results were published in a previous paper.

Table 13-2 Outcomes reported in RCTs comparing denosumab (Prolia®) to bisphosphonates

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Men with increased fracture risk											
NCT01575873 trial											
Saag, 2018[120] Argentina, Belgium, Canada, Columbia, Czech Republic, Denmark, France, Germany, Hungary, Mexico, Netherlands, Poland, Russia, Spain, South Korea, USA	Pro, randomised (1:1), double-blind	Men with osteoporosis and an increased risk of fracture (n=795)	✓ 12 mo	x	✓ 6, 12 mo (lumbar spine), 12 mo (total hip, femoral neck)	✓ 3, 4, 5, 6, 12 mo (sCTX, sP1NP)	x	✓ 12 mo	x	✓ 12 mo	✓ 12 mo
Saag, 2019[119] Argentina, Belgium, Canada, Columbia, Czech Republic, Denmark, France, Germany, Hungary, Mexico, Netherlands, Poland, Russia, Spain, South Korea, USA	Pro, randomised (1:1), double-blind	Men with osteoporosis and an increased risk of fracture (n=795)	✓ 24 mo	x	✓ 6, 12, 18, 24 mo (lumbar spine), 12, 24 mo (total hip, femoral neck, 1/3 radius)	✓ 10 days, 3, 4, 5, 6, 12, 24 mo (CTX, PINP)	x	✓ 24 mo	x	✓ 24 mo	✓ 24 mo
Postmenopausal women											

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
DAPS trial											
Freemantle, 2011[42] Canada, UK, USA	Pros, randomised (1:1), OL	Postmenopausal women (n=250)	✓ 24 mo	x	✓ 12, 24 mo (lumbar spine, total hip, femoral neck)	✓ 12, 18, 24mo (sCTX, P1NP)	x	✓ 24 mo	x	✓ 24 mo	✓ 24mo
Kendler, 2011[106] Canada, UK, USA	Pros, randomised, OL	Postmenopausal women (n=250)	x	x	12 mo (lumbar spine, total hip, femoral neck)	✓ 12mo (sCTX, uNTX)	x	✓ 12 mo	x	✓ 12 mo	✓12 mo
DECIDE trial											
Brown, 2009[40] Australia, Brazil, Canada, Germany, Spain, USA	Pros, randomised, double-blind	Postmenopausal women (n=1,189)	✓ 12 mo	x	✓ 6, 12 mo (total hip, lumbar spine, femoral neck)	✓ 6, 12 mo (sCTX, P1NP)	x	✓ 12 mo	x	✓ 12 mo	✓ 12 mo
NCT00043186 trial											
Lewiecki, 2007[109] USA	Pros, randomised, double-blind	Postmenopausal women (n=412)	x	x	✓ 1, 3, 6, 12, 18, 24 mo (lumbar spine, total hip) 6, 12, 18, 24 mo (distal 1/3 radius, total, body)	✓ 1, 3, 6, 12, 15, 18, 21, 24 mo (sCTX, uNTX, B-ALP)	x	✓ 24 mo	x	✓ 24 mo	x

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
McClung, 2006[111] USA	Pros, randomised, double-blind	Postmenopausal women (n=412)	✓ 12 mo	x	✓ 1, 3, 6, 12 mo (lumbar spine, total hip, 6, 12 mo (distal 1/3 radius, total body)	✓ 3d, 1, 2, 3, 4, 5, 6, 6-3d, 7, 8, 9, 10, 11, 12 mo (sCTX) 1, 3, 6, 9, 12mo (sB-ALP)	x	✓ 12 mo	x	✓ 12 mo	x
Miller, 2008 [112] USA	Pros, randomised, treatment blinded (one cohort OL)	Postmenopausal women (n=412)	✓ 48 mo	x	✓6, 12, 18, 24, 36, 48 mo (lumbar spine, total hip, distal 1/3 radius)	✓ 6, 12, 18, 24, 30, 36, 42, 48 mo (sCTX, B-ALP)	x	✓ 48 mo	✓36, 48 mo	✓ 48 mo	x
NCT00293813 trial											
Seeman, 2010[121] Argentina, Australia, Canada, France, USA	Pros, randomised (1:1:1), double-blind	Postmenopausal women (n=247)	x	x	✓ 6, 12 mo (total, trabecular, cortical, cortical thickness)	✓ 1, 3, 6, 7, 9, 12 mo (sCTX, sP1NP)	x	✓ 12 mo	x	x	✓ 12 mo
Zebaze, 2014[125] Argentina, Australia, Canada, France, USA	Pros, randomised, double-blind	Postmenopausal women (n=247)	x	x	x	✓ 3 mo (sCTX)	x	x	x	x	x
STAND trial											

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Kendler, 2010[107] Canada, France, USA	Pros, randomised, double-blind	Postmenopausal women (n=504)	✓ 12 mo	x	✓ 6, 12, 24 mo (total hip, femoral neck, lumbar spine, 1/3 radius),	✓ 1, 3, 6, 9, 12 mo (sCTX, sP1NP)	x	✓ 12 mo	x	✓ 12 mo	✓12 mo
Independent studies											
Anastasilakis, 2015[97] Greece	Interventional, randomised, OL	Postmenopausal women (n = 58)	x	x	✓ 12 mo (lumbar spine)	✓ 3, 6, 12mo (tALP, CTX, P1NP)	x	x	x	x	x
Beck, 2008[98] Germany, USA	Pros (post hoc analysis), randomised (1:1:1), blind for denosumab and placebo	Postmenopausal women (n = 116)	x	x	✓ 24 mo (femoral neck, narrow neck, intertrochanter and femoral shaft)	x	x	x	x	x	x
Brown, 2014[41] France, UK, USA	Pros (post hoc analysis or Recknor 2013 and Roux 2014), randomised, OL	Postmenopausal women (n=1,703, population was not counted as it is a posthoc analysis of two other trials)	✓12 mo	x	✓ 12 mo (total hip, femoral neck, lumbar spine)	✓ 1, 6, 12 mo (sCTX)	✓12 mo	✓ 12 mo	x	✓ 12 mo	x

Author, year, country publication	Study design	Population (n)	Primary effectiveness		Secondary effectiveness			Safety			Compliance
			Fractures	HRQoL	BMD	BTM	Fracture risk	Listed AE	AE associated with discontinuation	Total mortality	
Miller, 2016[113] Australia, Belgium, Canda, Denmark, Poland, Spain, USA	Pros, randomised, double-blind	Postmenopausal women (n=643)	✓ 12 mo	x	✓ 12mo (total hip, femoral neck, lumbar spine, 1/3 radius)	✓1, 3, 6, 7, 9, 12 mo (sCTX, sP1NP)	x	✓ 12mo	x	✓ 12mo	x
Recknor, 2013[117] France, Poland, Spain, UK, USA	Pros, randomised (1:1), OL	Postmenopausal women (n=833)	x	x	✓ <12, 12, ≤48 mo (total hip, femoral neck, lumbar spine)	✓ 1, 6 mo (sCTX, in a subset of patients)	x	✓ 12 mo	x	✓ 12 mo	✓ 12 mo
Roux, 2014[118] Australia, Austria, Canada, France, Germany, Greece, Italy, Netherlands, Spain, UK, USA	Pros, randomised (1:1), OL	Postmenopausal women (n=870)	x	x	✓ 12 mo (total hip, femoral neck, lumbar spine)	✓1, 6 mo (sCTX)	x	✓ 12 mo	x	✓ 12 mo	✓ 12 mo

Abbreviations

AE: adverse events, **BMD:** bone mineral density, **BTM:** bone turnover marker, **DAPS:** denosumab adherence preference satisfaction, **DIRECT:** denosumab fracture intervention randomised placebo controlled trial, **HRQoL:** health-related quality of life, **OL:** open label; **Pros:** prospective, **Retro:** retrospective; **sB-ALP:** serum bone-specific alkaline phosphatase, **sCTX:** serum C-terminal telopeptide of type 1 collagen, **sNTX:** serum N-terminal telopeptide of type 1 collagen, **sP1NP:** serum procollagen type 1 propeptide, **tALP:** total alkaline phosphatase, **TRAP:** tartare-resistant acid phosphatase, **uNTX:** urine N-terminal telopeptide of type 1 collagen.

14 Appendix C: Economic evaluation study extraction

Table 14-1 Characteristics of the included studies on health economic evaluations

Study	Country	Patient characteristics	Intervention	Comparator(s)	Costing Year	Time horizon	Perspective	Patient subgroup(s)
Chau, 2012[154]	Canada	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Risedronate - Raloxifene - No treatment	2010	Lifetime	Government payer	Postmenopausal women - High risk (women with at least two of: >70 years; T-score ≤-3.0 SD; previous vertebral fractures) - Age 75+ - Intolerant or contraindicated to oral bisphosphonates
Coyle, 2019[151]	Canada	Postmenopausal women - 70+ - No previous fracture - Tolerate bisphosphonates	Denosumab (Prolia®)	- Alendronate - Etidronate - Risedronate - Zoledronate - No treatment	2017	Lifetime	Societal	Age cohorts: - 65–69 - 70–74 - 75–79 - 80–84 - 85–89 - 90+
Darbà, 2015[155]	Spain	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Strontium ranelate - No treatment	2013	Lifetime	Government payer	Fracture status - Previous fractures - No previous fractures

Study	Country	Patient characteristics	Intervention	Comparator(s)	Costing Year	Time horizon	Perspective	Patient subgroup(s)
de Waure, 2014[156]	Italy	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Zolendronate - PTH - Teriparatide - Strontium ranelate	2009	Lifetime	Government payer	Age cohorts - 55–64 - 65–74 - 75+
Hiligsmann & Reginster, 2010[150]	Belgium	Postmenopausal women	Denosumab (Prolia®)	No treatment	2009	Lifetime	Government payer	- 60–80 years of age (T-score ≤ -2.5) - Prevalent vertebral fracture
Hiligsmann & Reginster, 2011[157]	Belgium	Postmenopausal women	Denosumab (Prolia®)	- Risedronate - Alendronate	2009	Lifetime	Government payer	Age cohort 60–80 years of age Fractures Prevalent vertebral fracture
Jönsson, 2011[158]	Sweden	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Risedronate - Strontium ranelate - No treatment	2008	Lifetime	Societal	- With and without cost in added life years - With and without prior morphometric vertebral fractures
Karnon, 2016[159]	Australia	Postmenopausal women	Denosumab (Prolia®)	Alendronate	2015	10 years	Government payer	NR

Study	Country	Patient characteristics	Intervention	Comparator(s)	Costing Year	Time horizon	Perspective	Patient subgroup(s)
Le, 2019[152]	US	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Etidronate - Risedronate - Zoledronic acid - Teriparatide - Abalopatride - No treatment	2017	10 years	Third-party payer or potential inclusion of government payment	- Low risk of fracture (50–65 years without previous fracture) - Medium risk of fracture (75+ years without previous fracture) - High risk of fracture (75+ years with previous fracture) - Very high risk of fracture (75+ years with previous fracture and total hip T-score ≤-2.5) - Experienced hip fracture (experienced hip fracture during the 10- year period)

Study	Country	Patient characteristics	Intervention	Comparator(s)	Costing Year	Time horizon	Perspective	Patient subgroup(s)
Makras, 2015[153]	Greece	Men and women over 50 years of age	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Zoledronic acid - Strontium ranelate - PTH - Teriparatide - Bazedoxifene - Alfacalcidol - Calcium - Alendronate/ Cholecalciferol - Calcium/ Cholecalciferol - No treatment	2013	Lifetime	Third-party payer or potential inclusion of government payment	Age cohorts - 50–55 - 55–59 - 60–64 - 65–69 - 70–74 - 75–79 - 80–84 - 85–89 - 90+ Gender - Men - Women
Marques, 2016[137]	Portugal	Men and women over 50 years of age with osteoporosis	Denosumab (Prolia®)	- Alendronate - Zoledronic acid - Teriparatide - No treatment	2013	Lifetime	Societal	NR
Parthan, 2013[161]	US	Postmenopausal women	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate	2012	Lifetime	Third-party payer or potential inclusion of government payment	Age Cohort 75+ Other High risk patients

Study	Country	Patient characteristics	Intervention	Comparator(s)	Costing Year	Time horizon	Perspective	Patient subgroup(s)
Parthan, 2014[160]	Sweden	Men aged over 75 years of age	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Zoledronate - Strontium ranelate - Teriparatide	2012	Lifetime	Government payer	NR
Silverman, 2015[162]	US	Men aged ≥75 years; T-score = -2.12; vertebral prevalence fracture = 23%	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Teriparatide - Zoledronate	2013	Lifetime	Third-party payer or potential inclusion of government payment	NR
Ström, 2013[163]	UK	Postmenopausal women age ≥50 years	Denosumab (Prolia®)	- Alendronate - Risedronate - Strontium ranelate - No treatment	2010	Lifetime	Government payer	NR

Abbreviations
NR: not reported.

Table 14-2 Evidence table for the included studies on health economic evaluations

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Chau, 2012[154]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states [a] - Well - Hip fracture - Vertebral fracture - Wrist fracture - Other osteoporotic fractures - Post-hip fracture - Post-clinical vertebral fractures - Dead	- Inclusion of gastrointestinal adverse events for use of alendronate or risedronate - Inclusion of cellulitis adverse events for use of denosumab - Variation in persistence of denosumab, health state parameters, cost, time horizon, efficacy and discount rates	5%	- FREEDOM study trial - Ontario Drug Benefit Program Formulary - Ontario Case Costing Initiative - Statistics Canada - Canadian Multicentre Osteoporosis Study (CaMos) - Various literature	EQ-5D HUI3	Cost per QALY gained
Coyle, 2019[151]	CUA in Markov cohort model (Monte Carlo simulated probabilistic analysis as base case) Cycle length 1 year Treatment duration 5 years	Health states - No previous fracture - Hip fracture (post-fracture year 1) - Vertebral fracture - Wrist fracture - Previous fracture - Dead	- Variation in discount rates, offset time - Additional non-osteoporosis health care cost	1.5%	- Ontario Drug Benefit Formulary - 2014 Canadian Community Health Survey - Ontario Case Costing Initiative - Institute for Clinical Evaluative Sciences - Provincial Ministry of Health - Canadian Multicentre Osteoporosis Study (CaMos) - Other various literature	Canadian Community Health Survey	Cost per QALY gained

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Darbà, 2015[155]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states - Well - Wrist fracture - Hip fracture - Vertebral fracture - Other osteoporotic fracture - Post-vertebral fracture, post-hip fracture - Dead	- T-score ≤2.5 - Variation in age at treatment initiation, previous fracture status - Extrapolation of treatment duration to 10 years - Multivariate sensitivity analysis - PSA	3%	- FREEDOM study trial - Various literature	EQ-5D	Cost per QALY gained Life-years gained
de Waure, 2014[156]	CEA in Markov cohort model Cycle length 6 months Treatment duration 3 years	Health states - Healthy (no fractures) - Hip/ femoral fracture - Vertebral fracture - Other fractures - 6 months after hip/femoral fracture; period following vertebral wrist fracture - Dead	PSA	3%	- National Institute for Statistics - National Hospitalisations Database - FREEDOM study trial - NICE - Diagnosis Related Groups - Various literature	EQ-5D[b]	Cost per QALY gained
Hiligsmann, 2010[150]	CEA in Markov microsimulation model Cycle length 1 year Treatment duration 3 years	Health states - No fracture - Wrist fracture - Hip fracture - Vertebral fracture - Other fractures - Death	- Variation in discount rates, fracture disutility, cost and risk, denosumab persistence and offset time - PSA	Cost = 3%, QALYs = 1.5%	- FREEDOM study trial - Belgian literature - National Institute of Statistics - Various literature	EQ-5D	Cost per QALY gained

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Hiligsmann. 2011[157]	CEA in Markov microsimulation model Cycle length 6 months Treatment duration 3 years	Health states - No fracture - Wrist fracture - Hip fracture - Clinical vertebral fracture - Other fracture - Post- wrist fracture - Post- hip fracture - Post- clinical vertebral fracture - Post- other fracture - Death	- Variation in discount rates, fracture risk, cost, disutility - No excess mortality after hip and vertebral fractures - No excess mortality after vertebral fractures	Cost = 3%, QALYs = 1.5%	- FREEDOM study trial - US National Health and Nutrition Examination Survey (NHANES) - National Institute of Statistics - Belgian literature - Various literature	EQ-5D	Cost per QALY gained
Jönsson, 2011[158]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states - Well - Hip fracture - Vertebral fracture - Wrist fracture - Other fracture c - Post-hip fracture - Post-vertebral fracture - Death	- Inclusion of gastrointestinal adverse events associated with alendronate and risedronate - Variation in discount rates, offset time - Reduction in time horizon to 10 years, disutility from fracture by 10%	3%	- FREEDOM study trial - European Prospective Osteoporosis Study - Various literature	EQ-5D	Cost per QALY gained

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Karnon, 2016[159]	CEA in Markov cohort model Cycle length 1 year Treatment duration 5 years	Health states - No major fracture - New major non-hip fracture - New hip fracture; previous major non-hip fracture - Previous hip fracture - Dead	- Variation in prices of denosumab, fracture cost discount rates, and utility - Cost-effectiveness acceptability curve - Denosumab vs no treatment patients	5%	- FREEDOM study trial - Pharmaceutical Benefits Scheme (PBS) - Australian life tables - Various literature	EQ-5D[b]	Cost per QALY gained
Le, 2019[152]	CEA in discrete event simulation (DES) Cycle length 1 year Treatment duration 5 years	Clinical events - Hip fracture - Vertebral fracture - Wrist fractures - Non-hip non-vertebral fracture - Entering nursing home after hip fracture - Death due to hip fracture - Death due to non-hip fracture	- PSA	3%	- RED BOOK wholesale acquisition cost (WAC) - Various literature	NR	Cost per QALY gained
Makras, 2015[153]	CEA in Markov cohort model Cycle length 1 year Treatment duration 5 years	Health states - Well - Hip fracture - Vertebral facture - Wrist fracture - Other osteoporotic fracture - Post-hip fracture - Post-vertebral fracture - Dead	- Varying WTP and intervention thresholds for various age cohorts	NR	- National Organisation for Health Care Services Provision - Published Greek literature - Various literature	NR	Cost per QALY gained

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Marques, 2016[137]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states - Well - forearm fracture - vertebral fracture - Hip fracture - Other fracture - Post-hip fracture - Post-vertebral fracture - Death	- Various willingness to pay scenarios and age cohorts	NR	- Portuguese Statistics Institute - Various literature	EQ-5D	Cost per QALY gained
Parthan, 2013[161]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states - Well - Hip fracture - Vertebral fracture - Other osteoporotic fracture - Post-hip fracture - Post-vertebral fracture - Death	- Variation in efficacies, cost, utilities, persistence ratio - PSA	3%	- FREEDOM trial - NICE - Marketscan Database Analysis - National Hospital Discharge Survey - Healthcare Costs and Utilisation Project - Various literature	EQ-5D	Cost per QALY gained
Parthan, 2014[160]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years 2 years (teriparatide)	Health states - Well - Hip fracture - Vertebral fracture - Other osteoporotic fracture - Post-hip fracture - Post-vertebral fracture - Death	- Variation in relative risk of hip fracture, offset time - PSA	3%	- NICE - Various literature - Skåne Region	EQ-5D	Cost per QALY gained

Study	Model	Health State(s)	Sensitivity Analysis	Discount rate	Source(s)	QoL Measure(s)	Evaluation Outcome(s)
Silverman, 2015[162]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years 2 years (teriparatide)	Health states - Well - Hip fracture - Vertebral fracture - Other osteoporotic fracture - Post-hip fracture - Post-vertebral fracture - Death	- Variation in relative risk of hip fracture, therapy costs, offset time - PSA	3%	- ADAMO trial - Various literature	EQ-5D[b]	Cost per QALY gained
Ström, 2013[163]	CEA in Markov cohort model Cycle length 6 months Treatment duration 5 years	Health states - Well - Hip fracture - Vertebral fracture - Forearm fracture - Other fractured - Post-hip fracture - Post-vertebral fracture - Death	- Inclusion of gastrointestinal adverse events - Variation in offset time after denosumab - Reduction in time horizon to 10 years	3.5%	- FREEDOM study trial - Various literature	EQ-5D	Cost per QALY gained

Abbreviations

ADAMO: 'A multicentre, randomised, double-blind, placebo in males, with osteoporosis', **CEA**: cost-effectiveness analysis, **CUA**: cost-utility analysis; **EQ-5D:** EuroQol- 5 Dimension, **HUI3:** Health utilities index mark 3, **FREEDOM**: fracture reduction evaluation of denosumab in osteoporosis every 6 months, **HUI3**: health utilities index mark 3, **NICE**: National Institute for Health and Care Excellence, **NR**: not reported, **PSA**: probability sensitivity analysis, **QALY**: quality-adjusted life year, **VTE**: venous thromboembolism, **WTP**: Willingness to pay.

Explanatory Notes

EQ-5D corresponds to an analytical tool which evaluates five dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

[a] Additional health states, VTE and breast cancer, were included when raloxifene selected as comparator.

[b] EQ-5D not explicitly reported in the study, but inferred from citations in the publications.

[c] Other fractures: rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures.

[d] Other fractures: pelvis, tibia (excluding ankle), shoulder girdle, rib and other femoral fractures considered to be sites of fracture due to osteoporosis.

15 Appendix D: List of excluded trials at full text

Wrong study design

1) Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen IfQuWi. A systematic guideline search and appraisal, as well as extraction of relevant recommendations for a DMP "osteoporosis": Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen, 2016.
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6) Camacho PM, Petak SM, Binkley N, et al. American association of clinical endocrinologists/american college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update executive summary. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2020 doi: 10.4158/gl-2019-0524 [published Online First: 2020/04/28]
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