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Health Technology Assessment (HTA)

HTA Scoping Report Protocol

Title	Vertebroplasty or Kyphoplasty in Patients with Symptomatic Osteoporotic Vertebral Compression Fractures Unresponsive to Non-Surgical Treatment

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Executive Summary

Osteoporotic vertebral compression fractures (OVCF) can cause debilitating pain, which reduces activity and quality of life, and may require inpatient care. Percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PBK) aim to treat the pain associated with symptomatic OVCFs by injecting cement into a fractured vertebra. There is ongoing debate in both the international scientific field and among policy makers for these procedures. In light of this controversy, the Swiss Federal Office of Public Health is re-evaluating the indications for PVP and PBK.

This scoping report aims to determine the feasibility of conducting a Health Technology Assessment (HTA) evaluation of PVP and PBK based on the volume, nature, and characteristics of the primary research identified during the scoping phase.

A systematic literature search was conducted in eight biomedical databases, in addition to clinical trial databases and speciality websites. The search was designed to identify randomized controlled trials (RCT) that compare the use of PVP and PBK with non-surgical treatments or sham procedures in patients with painful OVCFs. Eligible populations for PBK were further restricted to patients with acute fractures of less than eight weeks, based on the current reimbursement listing.

From 8,526 search results, 17 unique RCTs were suitable for inclusion (12 for PVP, 5 for PBK). Existing health economic models are predominantly based on RCTs published up to 2014. Several studies have been published since then, which may impact the cost-effectiveness of the interventions. There were limited social, ethical, legal and organisational issues identified in the database searches.

The authors conclude that there is sufficient clinical evidence to review the safety, efficacy, and effectiveness of PVP and PBK for painful OVCFs in a full HTA, noting that lower levels of evidence may be included in the full evaluation in the absence of RCTs. If an HTA is conducted for PVP, the analysis will be stratified by fracture age into acute (up to eight weeks) or non-acute (greater than eight weeks) fractures, in line with the current restrictions on PBK and similar reimbursement criteria used internationally.

Zusammenfassung

Osteoporotische Wirbelkompressionsfrakturen (OWF) können lähmende Schmerzen verursachen, welche die Aktivität und Lebensqualität beeinträchtigen und eine stationäre Versorgung erfordern. Die perkutane Vertebroplastie (PVP) und die perkutane Ballonkyphoplastie (PBK) zielen darauf die mit symptomatischen OWF verbundenen Schmerzen durch Injektion von Zement in den gebrochenen Wirbel zu behandeln. Sowohl in der internationalen wissenschaftlichen Literatur als auch in den Erstattungsrichtlinien sind diese Leistungen umstritten. Angesichts dieser Kontroverse prüft das Bundesamt für Gesundheit die Indikationen für PVP und PBK neu.

Dieser Scoping-Bericht hat zum Ziel die Durchführbarkeit eines Health Technology Assessment (HTA) für PVP und PBK zu ermitteln, und zwar aufgrund der Menge und der Qualität der vorhandenen Primärliteratur, die während der Scoping-Phase identifiziert wurden.

Eine systematische Literaturrecherche wurde in acht biomedizinischen Datenbanken, in Datenbanken klinischer Studien und auf Fachwebseiten durchgeführt. Die Suche war darauf ausgelegt, randomisierte kontrollierte Studien (randomized controlled trials, RCT) zu identifizieren, die bei Patientinnen und Patienten mit schmerzhaften OWF die Anwendung von PVP und PBK mit nicht-chirurgischen Behandlungen oder Placeboverfahren vergleichen. Die für PBK in Frage kommenden Populationen wurden aufgrund der aktuellen Erstattungsliste weiter eingeschränkt, und zwar auf Patientinnen und Patienten mit akuten, weniger als acht Wochen alten Frakturen.

Unter 8 526 Suchergebnissen waren 17 RCTs für den Einschluss geeignet (12 zu PVP, 5 zu PBK). Die bestehenden gesundheitsökonomischen Modelle basieren überwiegend auf bis 2014 veröffentlichten RCTs. Seitdem wurden mehrere Studien publiziert, die sich auf das Kosten-Nutzen-Verhältnis der Eingriffe auswirken können. Bei den Datenbankrecherchen wurden nur begrenzt soziale, ethische, rechtliche und organisatorische Aspekte identifiziert.

Die Autoren kommen zum Schluss, dass es genügend klinische Evidenz gibt, um die Sicherheit, Effizienz und Wirksamkeit von PVP und PBK für schmerzhafte OWF in einem vollständigen HTA zu überprüfen. Allerdings kann Evidenz niedrigen Grades in die vollständige Bewertung einbezogen werden, wenn keine RCTs vorliegen. Wenn ein HTA für PVP durchgeführt wird, wird die Analyse nach Frakturalter in akute (bis zu acht Wochen alte) und nicht-akute (mehr als acht Wochen alte) Frakturen unterteilt, was den derzeitigen schweizerischen Beschränkungen und ähnlichen internationalen Erstattungskriterien entspricht.

Synthèse

Les fractures vertébrales ostéoporotiques par compression (FVOC) peuvent entraîner une douleur débilitante, réduisant ainsi l'activité et la qualité de vie, et nécessiter une prise en charge stationnaire. La vertébroplastie percutanée (VP) et la cyphoplastie percutanée par ballonnets (CPB) visent à traiter la douleur associée aux FVOC symptomatiques en injectant du ciment dans une vertèbre fracturée. Ces deux interventions font actuellement débat, aussi bien dans la littérature scientifique internationale que du point de vue des politiques de remboursement. Au vu de cette controverse, l'Office fédéral de la santé publique réévalue les indications de la VP et de la CPB.

Le présent rapport de *scoping* vise à déterminer s'il est possible de soumettre la VP et la CPB à une évaluation de type ETS (« évaluation des technologies de la santé »). Il se fonde pour cela sur le volume et la qualité des recherches originales identifiées lors de la phase de *scoping*.

Une recherche systématique de la littérature disponible a été effectuée dans huit bases de données biomédicales, dans des bases de données d'essais cliniques et sur des sites internet spécialisés. Il s'agissait d'identifier des essais contrôlés randomisés (ECR) qui comparent l'utilisation de la VP et de la CPB avec des traitements non chirurgicaux ou des interventions placebo chez des patients présentant une FVOC douloureuse. Les populations éligibles à la CPB ont en outre été restreintes aux patients présentant des fractures aiguës de moins de huit semaines, conformément à la liste de remboursement actuelle.

Parmi les 8526 résultats de recherche, 17 ECR uniques sont utilisables pour l'analyse (12 pour la VP et 5 pour la CPB). Les modèles existants en économie de la santé s'appuient principalement sur les ECR publiés jusqu'en 2014. Plusieurs études publiées depuis lors pourraient avoir un impact sur le rapport coût-efficacité des interventions. Les problèmes sociaux, éthiques, juridiques et organisationnels identifiés en interrogeant les bases de données sont limités.

Les auteurs concluent que les données cliniques disponibles sont suffisantes pour évaluer, par une ETS complète, la sécurité et l'efficacité (théorique et réelle) de la VP et de la CPB pour le traitement des FVOC douloureuses. Ils notent qu'en l'absence d'ECR, des données moins probantes pourraient être intégrées à l'évaluation. Si une ETS est effectuée pour la VP, l'analyse distinguera les fractures aiguës (jusqu'à huit semaines) des fractures non aiguës (plus de huit semaines), conformément aux restrictions actuelles concernant la VP et aux critères de remboursement similaires appliqués dans le monde.

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Abbreviations and Acronyms

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Radiology
ADL	Activities of Daily Living
AE	Adverse events
AQoL	Assessment of Quality of Life
BMD	Bone mineral density
EUnetHTA	European Network for Health Technology Assessment
BI	Barthel Index
DPQ	Dallas Pain Questionnaire
EQ-5D	EuroQol 5-dimension questionnaire
EVOS	European Vertebral Osteoporosis Study
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR-QoL	Health-related quality of life
HTA	Health Technology Assessment
MCID	Minimum Clinically Important Difference
MRI	Magnetic resonance imaging
MMSE	Mini-mental state examination
MSAC	Medical Services Advisory Committee
NA	Not applicable
NICE	National Institute of Health and Care Excellence
nRCT	Non-randomised controlled trial
NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NSM	Non-surgical management
ODI	Oswestry Disability Index
OPAQ	Osteoporosis Assessment Questionnaire
OPLA	Operational local anaesthesia
OVCF	Osteoporotic vertebral compression fractures
PBK	Percutaneous balloon kyphoplasty
PICO	Population, intervention, comparator, outcome
PMMA	Polymethylmethacrylate

PVP	Percutaneous vertebroplasty
QALY	Quality-adjusted life year
QoL	Quality of life
QUALEFFO	Quality of Life Questionnaire of the European Foundation for Osteoporosis
RCT	Randomised controlled trial
RDQ	Roland-Morris Disability Questionnaire
SF-12/-36	Short Form-12/36
SOF	Strength of Function
SOF-ADL	Study of Osteoporotic Fractures—Activities of Daily Living
STIR	Short-TI Inversion Recovery
TCM	Traditional Chinese medicine
UK	United Kingdom
VAS	Visual analogue scale
WHO	World Health Organization

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Objective of the HTA Scoping Report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of vertebroplasty and balloon kyphoplasty for the treatment of painful osteoporotic vertebral compression fractures that do not respond to non-surgical treatment.

The process to evaluate health technologies involves multiple phases, 1) the pre-scoping phase, 2) the scoping phase, and 3) the Health Technology Assessment (HTA) phase. This document represents the outcome of the scoping phase.

In the scoping phase, a health technology is examined and a central research question is presented based on a systematic review of the literature. Operational key questions are formulated to determine the full scope of the HTA report. The target population, the appropriate comparator and the relevant health outcomes are defined.

The systematic literature search strategy informs the amount and types of studies extracted. The quantity and quality of the extracted evidence then determines whether an HTA report is commissioned. The objective of the HTA is to analyse individual study outcomes.

Conflicts of Interest

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

1. Policy Question and Context

Percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PBK) are used to treat vertebral fractures. These procedures are indicated for a range of fracture types, most commonly for the treatment of painful osteoporotic vertebral compression fractures (OVCF). In 2012/2013, 2,894 PVP procedures and 1,278 PBK procedures were conducted in patients with OVCFs in Switzerland. Considerable regional variation exists in age- and sex-standardised procedure rates, ranging from 1.0 to 10.1 per 10,000 persons across hospital service areas.[1] This regional variability is not wholly explained by population demographics or socioeconomic factors and may represent differences in clinician preferences.[1]

Internationally, there is an ongoing debate in (i) the scientific literature, (ii) clinical practice guidelines and (iii) reimbursement policies for PVP and PBK for patients with OVCFs:

i. In the literature on PVP, there are several randomised-controlled trials (RCTs) reporting conflicting results regarding pain, disability and quality of life outcomes for patients with OVCFs.[2-8]
ii. There is discord between clinical practice guidelines on vertebroplasty. Namely, the American Academy of Orthopaedic Surgeons (AAOS) recommend against treating OVCFs with vertebroplasty in 2010, whereas the American College of Radiology (ACR), the American Society of Neuroradiology, the American Society of Spine Radiology, the Society of Interventional Radiology, and the Society of NeuroInterventional Surgery have endorsed all vertebral augmentation procedures for OVCFs in June 2019.[9 10]
iii. The National Institute of Health and Care Excellence (NICE) in the United Kingdom recommends the use of PVP and PBK for patients with severe ongoing pain following the failure of non-surgical management, and in whom the pain has been confirmed to be at the level of the fracture.[11] In contrast, Australia removed PVP and PBK from the private reimbursement list in 2011 following a health technology assessment (HTA) evaluation, citing insufficient evidence of a clinical benefit and unacceptable cost-effectiveness.[12] Currently, PVP is reimbursed in Switzerland without restrictions, while PBK is reimbursed in patients with acute symptomatic fractures within eight weeks of onset, unresponsive to non-surgical treatment and with more than 15 degrees of localized kyphosis and/or more than one third loss of vertebral body height.[13]

In the context of the high degree of procedural variability, and the ongoing debate about the relative clinical and cost-effectiveness of PVP and PBK, an HTA evaluation has been commissioned to inform a policy decision on the continued reimbursement of these procedures.

2. Research Question

The research question of this assessment evaluates the safety, efficacy, effectiveness and cost-effectiveness of PVP and PBK for treating acute painful OVCFs compared to non-surgical treatments. It is further detailed in the PICO criteria in Section 5.

3. Medical Background

3.1 Health Condition

Osteoporosis is a progressive skeletal disease characterised by low bone mass (osteopenia) and disruption of the microarchitectural bone tissue. It is ranked in the top ten most important world diseases by the World Health Organization (WHO).[14] Patients with osteoporosis have increased bone fragility and a high susceptibility to fracture.[15 16] Osteoporosis with a pathological aetiology is referred to as primary osteoporosis. Disease caused by medication use such as corticosteroids, is referred to as secondary osteoporosis.[17] There is no cure. Treatment for osteoporosis is focused on limiting bone loss with medical therapy, hormone replacement therapy, and physical exercise. The disease is essentially asymptomatic until fractures arise.[16] OVCFs are the most frequent complication of osteoporosis, and are common in patients with rheumatoid arthritis.[18] Fractures can arise during activities of daily living without any specific trauma event, primarily occurring in the thoracolumbar region, and less frequently in the sacral and cervical regions.[19] Patients with OVCFs experience increased risk of subsequent vertebral fracture and death.[20]

Included trials have reported variable thresholds regarding fracture acuity.[2 5 21-23] Studies that have investigated interventional treatments for OVCFs have included variable cut-offs for “acute” fractures ranging from two to nine weeks.[2 5 22 23] Swiss guidelines that are currently used to limit services for PBK procedures set the cut-off for acuity at eight weeks, or fractures older than eight weeks that also have “active” signs on magnetic resonance imaging (MRI).[13 24] Fractures can be considered to be “active” on T2-Image or Short-TI Inversion Recovery (STIR) sequences.[94] “Active” fracture is indicated by bone oedema on the fractured vertebral body, defined as an increased intensity of signal at the STIR images and decreased signal intensity at the T1 weighted images.[25] Other MRI findings in acute OVCF can include: (i) hypointensity on T1-weighted images, (ii) hyperintensity or heterogeneous intensity on T2-weighted images, (iii) and hyperintensity on fat-suppressed T2-weighted images or on short-inversion time-inversion recovery images. Linear black signal may also be an indication of non-union.[26]

The estimated incidence of sacral insufficiency fractures ranges between one to five percent in at-risk populations, such as people who are inactive or bedridden for long periods of time, who diet excessively, or

have an eating disorder such as anorexia nervosa.[27] Osteoporotic fractures of the cervical spine are rare,[28] with a Canadian study estimating the incidence of cervical spine fractures to be 0.012% in the general population.[29] Patients most susceptible to OVCFs are older women with postmenopausal osteoporosis.[30 31] Elderly men with osteoporosis also have high susceptibility to OVCFs, however more women than men experience OVCFs due to longer life expectancy and a higher rate of osteoporosis.[32] The majority of osteoporotic fractures are asymptomatic and do not require treatment.[33]

Pain, defined as acute or chronic, is a key symptom of OVCFs. Acute pain is defined as that which arrives quickly, is severe, and is related to soft tissue damage. In this population, acute pain is thought to arise from fracture mobility, whereby changes in posture place different degrees of compression on the fracture.[2] Chronic pain is defined as that which persists beyond the expected healing time, arising as part of a disease process affecting the soft tissue.[34] One third of all vertebral compression fractures reportedly do not heal within a few months and become chronically painful.[35] Without effective treatment, OVCFs can lead to acute and chronic pain, impaired mobility, reduced quality of life and increased risk of death.[36] Impaired mobility in osteoporotic patients may accelerate bone loss.

Osteoporotic spinal deformity, also known as kyphosis, is another outcome of OVCFs. Fractures of the thoracolumbar vertebrae can, in severe cases, lead to loss of vertebral height, wedging of several thoracic vertebrae, and kyphotic deformity. Kyphosis is measured in percentage or degree of spinal curvature.[19] Kyphotic deformity is associated with loss of mobility and reduced quality of life.[37] In the context of an evaluation of PVP and PBK, kyphosis is a surrogate outcome and is thus not the focus of this review.

3.2 Incidence in Switzerland

Due to long life expectancy at birth and longevity after age 80, Switzerland ranks second worldwide amongst countries with the highest proportion of elderly residents.[38] Switzerland has a high disease burden from osteoporosis, and as the population continues to age this burden is likely to increase. In 2010, the number of Swiss with osteoporosis (defined by WHO diagnostic criteria) in the at-risk population (age 50 years and over) was 458,547 (368,685 of 1,660,000 women; 89,862 of 1,381,000 men).[39] In that year, the incidence of major osteoporotic fracture in the at-risk population was 2,078 per 100,000 women and 773 per 100,000 men. Demographic projections estimate that the number of patients with osteoporosis in Switzerland are forecast to increase.[39] As previously stated, OVCFs are the most frequent complication of osteoporosis and an important cause of morbidity and mortality.[36]

4. Technology

4.1 Percutaneous Vertebroplasty (PVP)

PVP is the injection of cement, most often polymethylmethacrylate (PMMA), into a fractured vertebral body of the spine. The aim of the procedure is to relieve pain and strengthen the bone to prevent future fractures.[4] [11] Patients are given analgesic medication and a local anaesthetic, with or without conscious sedation, for the procedure. At times a bi-pedicular approach is taken whereby two needles are used, one either side of the pedicle, to inject cement into the same vertebral level to provide more even distribution.

4.2 Percutaneous Balloon Kyphoplasty (PBK)

PBK is a variant of PVP, involving the insertion of balloon-like devices called tamps into the vertebral body.[11] The balloon tamp is inserted through vertebral paracentesis with a needle cannula under image guidance, and the injection device connected. A larger needle cannula (usually 8-guage) is needed to allow for the balloon tamp to be inserted. There are at least two versions of the PBK procedure: (i) the balloon is inflated with bone cement (usually PMMA), until the normal height of the vertebral body is restored;[40] (ii) the balloon is inflated with fluid then removed, and cement injected into the cavity created.[41] PBK aims to reduce pain and restore fractured vertebrae to the normal vertebral height.[11]

As with PVP, the most common complications are cement leakage and adjacent vertebral fracture.[42] [43] While it is not a requirement of the procedure,[44] many PBK patients receive general anesthesia and remain in hospital overnight.[45]

Due to limited evidence in Switzerland, the Swiss Federal Office of Public Health implemented mandatory nationwide reporting of each PBK procedure performed. To support government decision-making, the SWISSspine registry was started in March 2005 to assess the real-world safety and effectiveness outcomes of PBK.[46]

PBK is currently reimbursed in Switzerland for OVCFs only for patients with fresh thoracolumbar fractures (less than 8 weeks duration) associated with pain VAS ≥ 5 and significant deformation such as thoracic kyphosis >15° or lumbar kyphosis >10°.[13]

4.3 Conduct of the Procedures

PVP or PBK is a treatment option for patients who have severe, ongoing pain after a recent vertebral fracture, where the level of fracture is confirmed by physical examination and imaging, and in whom medical pain management is ineffective.[11] Which technique is conducted on a specific patient is dependent on the fracture

type and location, bone quality, and the patient's activity level.[47] With a wider spectrum of indication, PVP is used to treat simple compression fractures; where there is kyphotic deformity, especially in the thoracolumbar junction, PBK may be the preferred option.[48 49] A Swiss healthcare trust reports that the PVP procedure (approximately 2,300 per year) is most commonly performed in a day surgery suite with less than 13 percent of procedures being performed in an ambulatory setting each year,[50] while all PBK (approximately 1000 per year) are conducted in an inpatient setting in Switzerland.[51 52] The practitioner performing the intervention differs between procedures. In Switzerland an interventional radiologist usually performs PVP, while a qualified spinal surgeon is able to perform PBK.[13 24] Because these procedures are performed under fluoroscopic guidance a hospital must have high-quality imaging equipment available.[53] Materials required include radiopaque bone cement and a complex vertebroplasty or kyphoplasty delivery system.[54] Patients must recline in a supine position for one to two hours post-procedure while the cement hardens. A short-term prescription for narcotic analgesics may be given for immediate procedure-site pain.[54]

Technical differences between the two procedures include the insertion of a balloon tamp during PBK (either deflated or left in place),[40 41] longer operating time for PBK,[42] a more expensive delivery system (additional US$3,000 for PBK), and sometimes the necessity for an overnight stay for PBK, resulting in PBK being more costly than PVP (according to data from the USA).[44] However, PBK can also be conducted as a day surgery procedure under neuroleptic IV sedation and may take no longer to perform than PVP (clinical reviewer, personal communication).

Cement flow during these procedures cannot be completely controlled. Cement leakage and adjacent vertebral fracture are common complications of the procedures.[42] These complications can be asymptomatic and symptomatic, which is an important distinction for assessment of safety.[55] Leakage is commonly reported and can lead to complications if cement enters the spinal canal, lungs, or veins.[56]

New fractures, especially in adjacent vertebrae, are commonly recorded in RCTs. [57 42 55] New OVCFs either remain asymptomatic or require subsequent treatment by PVP or PBK.

Potential adverse reactions for both procedures exist due to needle insertion and include bleeding, systemic infection, and damage to neural structures.[11]

4.4 Incidence of the Procedures in Switzerland

A population-based analysis reported that 2,894 PVP procedures and 1,278 PBK procedures were conducted in patients with OVCFs in Switzerland in 2012/2013. In addition to OVCFs, other important indications for PVP and PBK are trauma and cancer diagnoses.[46 50] There was considerable regional variation in age- and sex-standardised procedure rates, ranging from 1.0 to 10.1 per 10,000 persons across hospital service areas.[1] Hospital service areas located in the greater Bern area, Uri and Schwyz, had the

highest PVP/PBK age- and sex-standardised procedure rates (6.9-10.1 per 10,000 persons). The lowest PVP/PBK procedure rates (1.0-2.0 per 10,000 persons) were found in Zurich, Jura, Basel, Glarus, Geneva and the western Valais.[1]

More recent Swiss hospital data from 2015, reported 2,073 PVP and 1,052 PBK procedures performed in individuals age 17 and older, although this data was not specific to OVCFs. The most recent estimates also reported a large variation in the incidence of PVP (range 0-4.3 per 10,000) and PBK (range 1.0-10.8 per 10,000) among 20 hospital regions in Switzerland.[58 59]

Two-thirds of this variation cannot be explained by demographic or socio-economic factors, and as it is unlikely to be driven by regional variation in patient need or preference, most of the observed variation is likely to be unwarranted and due to different practices of physicians.[1]

4.5 Alternative Technologies Considered for this Population

The alternative treatment for this population is non-surgical treatment requiring a comprehensive, multifaceted approach. Primary in this approach are non-invasive treatments such as analgesics (with or without opiates), bed rest, back braces, physiotherapy and lifestyle changes. Clinical practice guidelines recommend OVCF patients have non-surgical treatments before commencing surgical options.[60 61]

Medications most commonly used to treat OVCF-related pain include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, opioids, lidocaine patches and muscle relaxants.[33 62] Opioids can often relieve OVCF pain, however the side effects can be serious, including constipation, nausea and cognitive impairment. Patients with OVCF pain may respond to NSAIDs if the pain relates to inflammation in the soft tissue. Problematic side effects of NSAIDs are stomach ulcers, nausea, and gastritis. If the patient's ability to perform daily functions improves, medications should be gradually reduced to avoid significant morbidity.[63]

Braces are used to support muscular deconditioning, promote appropriate posture, and provide neuromuscular re-education and comfort for OVCF patients. Bracing after fracture can be an important part of treatment, and in some cases, braces may provide enough support to allow natural healing. Each brace is individually tailored for patient comfort and function. As pain declines the brace should be worn less frequently before ceasing altogether.[63]

Physiotherapy begins with education of pain avoidance in activities of daily living. Exercise directed by a physiotherapist can reduce pain, build strength and prevent future fractures in OVCF patients.[64]

If non-surgical treatments fail to provide significant improvement, approaches such as nerve blocks and neuromodulation may be indicated.[41 65] These more invasive approaches can also serve as alternatives to PVP/PBK for the management of spinal pain in patients unsuitable for traditional surgical intervention. Nerve

blocking is infiltration of anaesthetic around a nerve to cause interruption of the pain signal travelling along the nerve, common examples are epidural block and spinal anaesthesia.[66] [67] Neuromodulation consists of electrical spinal stimulation to inhibit pain pathways. A subcutaneously implanted pulse generator creates an electrical field around the spinal column and dorsal pathways, which interrupts the pain pathways.[68] [69]

4.6 Concomitant Treatments

Surgical and non-surgical approaches to managing OVCFs should be used in combination with medical treatment for underlying osteoporosis to prevent further bone loss.[70] Medical treatment for primary osteoporosis includes adequate intake of calcium and vitamin D, followed by pharmacological treatments, or hormone replacement therapy.[16] The choice of pharmacological treatment is influenced by several factors, including whether the patient has primary or secondary osteoporosis. In general, pharmacological treatments should be used as concomitant therapy in patients aged 70 or older, with minimal trauma fracture/s, low bone density, and who are on prolonged, high dose corticosteroid treatment. Common pharmacological treatments include raloxifene, strontium ranelate and teriparatide medications for reducing bone loss. Bisphosphonate medicines may be used for the prevention of osteoporotic fractures, although their use is controversial and there have been reports of prolonged bisphosphonate therapy leading to atypical subtrochanteric fractures and jaw osteonecrosis.[71] Denosumab can be recommended for post-menopausal women for prevention of fractures, although its use is also under investigation for safety reasons. Hormone replacement therapy can be given to women at any stage of menopause and aims to preserve and increase bone mineral density.[72]

Physicians should also review any medicines or environmental factors that may contribute to falls in the elderly patient.[70]

5. PICO

5.1 Patients

Percutaneous Vertebroplasty

The patient population for the assessment of PVP includes patients with an OVCF that are non-responsive to non-surgical treatments. Vertebroplasty is currently reimbursed without restriction in Switzerland, so no limitations will be placed on the severity of pain, duration of fracture, or degree of kyphosis.[13] Use of PVP for other types of fracture, for example due to non-osteoporotic trauma or malignancy, is not the focus of this report.[13]

Percutaneous Balloon Kyphoplasty

The patient population for the assessment of PBK has been defined according to the Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung.[13] In osteoporotic patients, PBK is currently reimbursed for patients with thoracolumbar fractures less than eight weeks old, that are unresponsive to analgesics, have Pain (VAS ≥ 5), and deformation (i.e. thoracic kyphosis >15°, lumbar kyphosis >10°, and/or vertebral body height reduction of more than one third compared to adjacent bodies).[13 24]

In old fractures (defined as more than 8 weeks duration) in osteoporotic patients balloon kyphoplasty is recommended if the conditions mentioned above have been met, and additionally if the fracture has been shown to be “active” on MRI and feels painful to the patient.[13 24] If there are normal signs on MRI in an osteoporotic patient, balloon kyphoplasty is not indicated.[13 24] Detail on fracture indications on MRI is provided in Section 3.3: Conduct of the Procedures. Only osteoporotic fractures, not fractures arising from non-osteoporotic trauma or spinal tumours, are relevant to this investigation.[13 24]

5.2 Intervention

The procedures under investigation are PVP and PBK conducted under fluoroscopic guidance[53] (described in detail in Section 4 – Technology).

Procedural variations that may impact the clinical outcomes include the training background of the interventional radiologist or medical practitioner involved, the cement type (e.g. PMMA or calcium phosphate), and uni-pedicular or bi-pedicular approaches for insertion of cement into the vertebrae. These factors will be investigated in the full HTA report via subgroup analysis.

Concomitant procedures whereby another intervention is conducted along with the vertebral augmentation (i.e. PVP with pedicle screws, PBK with expandable devices) confound the effect of PVP/PBK and are not relevant to the present investigation. Vertebral augmentation will only be investigated in cases where the fracture has already occured.[73] Vertebral augmentation given as a prophylactic treatment will not be considered.

5.3 Comparator

Sham controls provide the best evidence for the relative safety and effectiveness of PVP and PBK. Sham procedures simulate PVP and PBK procedures but do not inject cement into fractured vertebrae. Patients receive the same anaesthetic, the same needles are inserted in fractured vertebrae, and the cement is prepared within the room so that the patient can smell the mixture.

Conservative, non-surgical treatment is the main unblinded comparator for both PVP and PBK. Patients in sham trials often also receive non-surgical treatments in addition to the sham. Non-surgical treatments require a comprehensive, multifaceted approach. Primary treatments include oral analgesics (with or without opiates), bed rest, back braces, physiotherapy and lifestyle changes. European guidelines recommend that patients undergo non-surgical treatments for at least three weeks before undergoing PVP or kyphoplasty procedures.[60]

5.4 Outcomes

Efficacy/effectiveness

The primary aim of PVP and PBK is to relieve debilitating pain associated with OVCFs, which limits physical function and decreases quality of life. In this context, the critical efficacy/effectiveness outcomes include pain, physical function and quality of life. For the HTA phase, RCT evidence compared to sham procedure or non-surgical treatment will provide the most robust evidence. Lower levels of evidence will not be included for these outcomes where adequate RCT data is available. Outcomes will be assessed at three time points: short term (post-operative up to three months), intermediate (up to 12 months), and long term (>12 months). Pain relief associated with PVP and PBK may be instantaneous, therefore no limitations were placed on the minimum follow-up duration for included studies. The durability of the treatment effect will be evaluated in trials with long-term follow-up (i.e. 12-24 months).

Surrogate outcomes related to fracture deformity (e.g. vertebral height loss and wedge angle) will be considered for inclusion in the HTA report only if insufficient evidence is identified for the primary patient-relevant outcomes (e.g. pain, mobility, quality of life).

Critical

Pain is the primary OVCF symptom that impacts quality of life. Pain related to spinal fracture is most commonly reported using visual analogue and numerical rating scales measured on a per-patient basis and presented as a mean difference across included patients.

Physical function can be impacted by both pain and kyphosis (i.e. abnormal rounding of the upper back) caused by OVCFs. Function can be measured using a variety of scales, including the Roland Morris Disability Questionnaire (RDQ) and Oswestry Disability Index (ODI). Measuring physical function with objective personal instruments such as pedometers, smart watches, smart phones and wearable fitness trackers is gaining popularity in clinical studies as a complement to subjective data collective in self-administered questionnaires and VAS. This form of data would be an acceptable measure of physical function in the assessment.

Quality of life (QoL) in studies of PVP and PBK has been measured using both generic scales (e.g. SF-36, EQ-5D) and disease-specific scales (e.g. Quality of Life Questionnaire of the European Foundation for Osteoporosis—QUALEFFO). Functional measures of QoL include discharge home, ability to execute activities of daily living, independent living or admission to nursing home accommodation.

Important

Concomitant analgesia usage, specifically long-term opioid use, is a surrogate outcome used to measure the effectiveness of an intervention at relieving pain.

Safety

While both are low risk procedures, PVP and PBK carry safety concerns related to cement leakage. All study designs (i.e. RCT, non-randomised studies and single-arm studies) are considered to be relevant for identifying safety issues related to PVP and PBK, however, only prospectively designed studies will be included due to the limitations associated with retrospective collection of safety data.

Critical

Serious adverse events (including cement leakage, infection) and **procedure-related mortality** are critical safety outcomes associated with the use of PVP and PBK. In this context, a serious adverse events is characterised as an event that is life-threatening, requires hospitalisation, is disabling or permanently damaging, requiring intervention, causes death, or any other event deemed serious by the study investigators.[74]

It has been hypothesised that internal fixation therapies such as PVP and PBK may increase the likelihood of **new symptomatic adjacent vertebral fracture** in patients with osteoarthritis.[75] Adjacent vertebral fracture may be measured clinically (i.e. symptomatic new fractures) or sub-clinically (i.e. radiographic evidence of new fracture). This review is only concerned with symptomatic adjacent fracture.

Important

Exposure to radiation (patient and physician) and **adverse events** are important safety outcomes.

Minimum Clinically Important Differences (MCID)

An indication of the MCIDs that will be considered when analysing the primary outcomes of pain, function and quality of life are listed in **Table 1**.

Table 1 Minimum Clinically Important Difference (MCID) in scores for the primary outcomes

Study ID	Study design, patient indication, patient or study sample size (n=), any differences in measures	Reported MCID
Oswestry Disability Index (ODI)		
Copay et al. 2008[76]	Data from Lumbar Spine Study database on n=427 patients undergoing spine surgery (decompression and spinal fusion, exact indication not reported).	12.81(scoring range 0–50)
Roland–Morris Disability Questionnaire (RDQ)		
Chandra et al 2014[77]	Guideline on vertebral augmentation, including 5 RCTs on patients with OVCFs.	2–3 (scoring range 0–23)
Ostelo et al. 2008[78]	Expert consensus and review of n=18 "empirical studies" on patients with lower back pain.	5 (scoring range 0–24)
Short Form 36 Medical Outcomes Study Questionnaire (SF-36)		
Copay et al. 2008[76]	Data from Lumbar Spine Study database on n=457 patients undergoing spine surgery (exact indication not reported).	1.16 (scoring scale 1–10)
EuroQOL 5-Dimension Questionnaire (EQ-5D)		
Walters & Brazier 2005[79]	Method review study of n=11 longitudinal studies and RCTs on patients with mixed indications only one of which was back pain.	0.08 median, 0.07 mean (scoring scale 0.59–1.00)
Numerical Rating Scale (NRS)		
Ostelo et al. 2008[78]	Expert consensus and review of n=18 "empirical studies" on patients with lower back pain.	Acute back pain 3.5, Chronic back pain 2.5 (scoring range 0–10)
Visual Analogue Scale (VAS)		
Ostelo et al. 2008[78]	Expert consensus and review of n=18 "empirical studies" on patients with lower back pain. Measures VAS out of 100.	15 (scoring range 0–100)

Abbreviations: **EQ-5D** = EuroQOL 5-Dimension Questionnaire, **MCID** = Minimum Clinically Important Difference, nRCT = non-randomised controlled trial, **NRS** = Numerical Rating Scale, **ODI** = Oswestry Disability Index, **OVCF** = Osteoporotic Vertebral Compression Fractures, **RCT** = randomised controlled trial, **RDQ** = Roland–Morris Disability Questionnaire, **SF-36** = Short Form 36 Medical Outcomes Study Questionnaire, **VAS** = Visual Analogue Scale.

Comparative cost-effectiveness

If warranted by the clinical investigation, an economic evaluation will be performed to compare the cost-effectiveness outcomes across PVP, PBK and non-surgical treatments. To ensure the applicability of the economic evaluation, the evaluation will be conducted using Swiss cost information (e.g. TARMED, DRGs, spezialitätenliste). Model and parameter uncertainties will be investigated by sensitivity analyses, and the

impact of any significant uncertainties will be interpreted in the Swiss context. A cost-utility analysis (CUA) is the most likely modelling approach, to evaluate Swiss Francs (CHF) per utility gained (via quality adjusted life year, QALY) between the use of PVP, PBK and the comparator.

Budgetary impact

The budgetary impact of removing PVP and PBK will be evaluated. The five-year projected impact of withdrawing PVP and PBK from their reimbursement list will be calculated in term of the net cost differences. Any uncertainties will be investigated by sensitivity analyses.

5.5 PICO-Box

Table 2 PICO criteria for PVP

P:	Osteoporotic patients with painful OVCF that does not respond to medical treatment *(Exclusions: fractures arising from non-osteoporotic trauma or spinal tumours)*
I:	PVP *(Exclusions: concomitant treatments including pedicle screw fixation, prophylactic augmentation)*
C:	Non-surgical treatment (i.e. optimal medical therapy, physiotherapy, bracing) or sham procedure
O:	**Efficacy/effectiveness:** • Pain • Physical function • Quality of life • Analgesia usage • Proportion of patients able to return to independent living compared to proportion requiring assisted accommodation (i.e. nursing homes) **Safety:** • Serious procedure-related adverse events • Other adverse events • New symptomatic adjacent vertebral fractures • Procedure-related mortality • Patient/physician exposure to radiation **Economics:** • Costs of PVP • Comparative cost-utility outcome of PVP against non-surgical treatments (incremental CHF per QALY gained) • Five-year projected budget impact of withdrawing PVP from the reimbursement list

S:	**Efficacy/effectiveness:** • RCTs • In the absence of randomised trials, other prospective comparative study designs will be considered *(Exclusions: narrative reviews, letters to the editor, author responses, case reports, single-arm studies)* **Safety:** • RCTs with at least 10 patients in each treatment arm • Prospective nRCTs with at least 10 patients in each treatment arm • Prospective case-series with at least 10 patients *(Exclusions: narrative reviews, letters to the editor, author responses, case reports)*

Table 3 PICO criteria for PBK

P:	1) Painful OVCF less than eight weeks old that does not respond to medical treatment, with the following features: • Pain (VAS ≥ 5) • Vertebral deformity: Thoracic kyphosis of more than 15 degrees, and/or lumbar kyphosis of more than 10 degrees, and/or vertebral height reduction of more than one third compared to adjacent bodies 2) Fractures older than eight weeks fulfilling the aforementioned pain and deformity criteria, as well as clear magnetic resonance imaging signs that the fracture is "active", i.e. bone oedema. *(Exclusions: fractures arising from non-osteoporotic trauma or spinal tumours)*
I:	PBK *(Exclusions: concomitant treatments including pedicle screw fixation, prophylactic augmentation, kyphoplasty with other expandable devices including Sky bone expander, stents etc)*
C:	Non-surgical treatment (i.e. optimal medical therapy, physiotherapy, bracing) or sham procedure
O:	**Efficacy/effectiveness:** • Pain • Physical function • Quality of life • Analgesia usage • Proportion of patients able to return to independent living compared to proportion requiring assisted accommodation (i.e. nursing homes) **Safety:** • Serious procedure-related adverse events • Other adverse events • New symptomatic adjacent vertebral fractures • Procedure-related mortality • Patient/physician exposure to radiation **Economics:** • Costs of PBK • Comparative cost-utility outcome of PBK against non-surgical treatments (incremental CHF per QALY gained)

	• Five-year projected budget impact of withdrawing PBK from the reimbursement list
S:	**Efficacy/effectiveness:** • RCTs • In the absence of randomised trials, other prospective comparative study designs will be considered *(Exclusions: narrative reviews, letters to the editor, author responses, case reports, single-arm studies)* **Safety:** • RCTs with at least 10 patients in each treatment arm • Prospective nRCTs with at least 10 patients in each treatment arm • Prospective case-series with at least 10 patients *(Exclusions: narrative reviews, letters to the editor, author responses, case reports)*

6. HTA Key Questions

For the evaluation of the technology the following key questions covering the central HTA domains, as designated by the EUnetHTA Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical and organisational aspects), are addressed:

1. Are PVP and PBK effective/efficacious compared to non-surgical treatments or sham procedure?
2. Are PVP and PBK safe compared to non-surgical treatments or sham procedure?
3. What are the costs of PVP and PBK?
4. How cost-effective is PVP and PBK compared to non-surgical treatments or sham procedure?
5. What is the budget impact of PVP and PBK?
6. Are there legal, social or ethical issues related to PVP and PBK?
7. Are there organisational issues related to PVP and PBK?

6.1 Additional Questions(s)

Key sub-questions of relevance to PVP and PBK have been informed by the European Network for Health Technology Assessment (EUnetHTA) HTA Core Model® (Version 3.0).[80] All sub-questions related to the key assessment domains (i.e. efficacy, effectiveness, safety, cost-effectiveness, ethical, patient/social, legal, organisational) were considered, however, only those deemed relevant in the context of a potential disinvestment from PVP and PBK were included.

6.2 Sub-Questions: Efficacy, Effectiveness and Safety

Minimally-invasive vertebral augmentation with PVP and PBK is used to treat OVCFs causing severe pain that do not respond to conventional medical therapy. PVP aims to relieve pain and stabilise the fracture, whereas PBK aims to additionally restore vertebral height, reducing the curvature of the spine. Important patient-relevant outcome measures include pain relief and improved function. Relevant sub-questions on safety and effectiveness from the EUnetHTA Core model (Version 3.0) are outlined in **Table 4** and **Table 5**.

Table 4 Sub-Questions: Safety

Topic	Research Question	Element ID
Patient safety	How safe is the technology in comparison to the comparator(s)?	C0008
Patient safety	Are there susceptible patient groups that are more likely to be harmed through the use of the technology?	C0005
Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	C0007
Occupational safety	What kind of occupational harms can occur when using the technology?	C0020

Table 5 Sub-Questions: Effectiveness

Topic	Research Question	Element ID
Mortality	Is there an expected beneficial effect of the technology on mortality?	D0001
Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	D0005
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	D0006
Function	What is the effect of the technology on body functions of patients?	D0011
Function	What is the effect of the technology on work ability?	D0014
Function	What is the effect of the technology on return to previous living conditions?	D0015
Function	How does the use of technology affect activities of daily living?	D0016
Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	D0012
Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	D0013
Change-in management	How does the technology modify the need for hospitalisation?	D0010

6.3 Sub-Questions: Costs, Cost-Effectiveness and Budget Impact

The relative cost-effectiveness of PVP and PBK will be considered in relation to non-surgical treatment. When appropriate, the cost-utility and cost-effectiveness results will be calculated using appropriate modelling techniques. Budget impact analysis will investigate the impact of withdrawing PVP and PBK from the Swiss reimbursement list. Expected changes in the overall compulsory basic health insurance, such as resources involved in technologies needed to supplement its use, will be considered, e.g. relative difference in inpatient bed-days required for PVP/PBK compared to non-surgical treatment. Key questions relevant to PVP/PBK related to costs, budget impact and cost-effectiveness are outlined in **Table 6**.

Table 6 Sub-Questions: Costs, Budget Impact and Cost-Effectiveness

Topic	Research Question	Element ID
Resource utilisation	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	E0001
Resource utilisation	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	E0002
Resource utilisation	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009
Resource utilisation	How does the technology modify the need for other technologies and use of resources?	D0023
Resource utilisation	What are the likely budget impacts of implementing the technologies being compared?	G0007
Measurement and estimation of outcomes	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?	E0005
Examination of costs and outcomes	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?	E0006
Characterising uncertainty	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?	E0010
Characterising heterogeneity	To what extent can differences in costs, outcomes, or 'cost-effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?	E0011
Validity of the model(s)	What methodological assumptions were made in relation to the technology and its comparator(s)?	E0013
Validity of the model(s)	To what extent can the estimates of costs, outcomes or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?	E0012

6.4 Sub-Questions: Legal, Social and Ethical Issues

There are limited legal issues related to the potential disinvestment of PVP or PBK from the compulsory basic health insurance scheme in Switzerland. Legal issues arising in the literature may relate to the legal requirements for providing accurate information about the procedure to the patient and to the provision of accurate information regarding who can consent to the procedure for an incompetent patient. However, these issues are only relevant to a policy decision to introduce a new procedure into the compulsory health insurance, therefore no sub-questions related to legal issues need to be investigated in the HTA report.

Issues arising in the literature pertaining to patient and social aspects may relate to appropriate communication with the patient about treatment choices, and the patient's perceptions and expectations about the procedure. Sub-questions related to patient and social aspects relevant to PVP/PBK are outlined in **Table 7**. Literature around the experience of patients and caregivers is limited. Collection of survey data from Swiss patients may be required in order to address these questions in the HTA report.

Table 7 Sub-Questions: Patient and Social Aspects

Topic	Research Question	Element ID
Patient perspective	What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology?	H0100
Patient perspective	What is the burden on care-givers?	H0002
Social group aspects	Are there groups of patients who currently don't have good access to available therapies?	H0201

Ethical issues described in the literature relate to the balance between benefit of receiving the intervention and possible harms, unintended consequences of the procedure, and a patient's right to exercise autonomy over receiving the intervention. Sub-questions related to ethical issues relevant to PVP/PBK are outlined in **Table 8**.

Table 8 Sub-Questions: Ethical Aspects

Topic	Research Question	Element ID
Autonomy	Is the technology used for individuals that are especially vulnerable?	F0005

6.5 Sub-Questions: Organisational Issues

Limitation or withdrawal of PVP and/or PBK from coverage in Switzerland could impact organisational factors such as work processes and patient flow due to the need for other treatment and resources for this patient group. Management issues and differences associated with the comparator treatment, non-surgical treatment, have been identified in the literature. Key questions related to patient and social aspects that are relevant to PVP/PBK are outlined in **Table 9**.

Table 9 Sub-Questions: Organisational Aspects

Topic	Research Question	Element ID
Health delivery process	How does the technology affect the current work processes?	G0001
Health delivery process	What kind of patient/participant flow is associated with removing the technology from basic health insurance?	G0100
Process-related costs	How does the technology modify the need for other technologies and use of resources?	D0023
Management	What management problems and opportunities will removing the technology cause?	G0008

7. Methodology Literature Search

7.1 Databases and Search Strategy

A systematic literature search was conducted to identify relevant literature to address the research questions and inform the PICO criteria for the HTA evaluation. Eight biomedical databases (PubMed, Embase, the Cochrane Library, CINAHL, York Centre for Reviews and Dissemination, CEA Registry, Econlit and Ethmed) were searched from inception up to 4 April 2019. In addition, ongoing or unpublished clinical trials were searched from the following databases: 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.

Search terms comprised a combination of keywords and medical subject headings (MeSH) relating to vertebroplasty, kyphoplasty and osteoporotic vertebral compression fractures. The full search strategy for each database is reported in Appendix A. No search filters were applied. All languages were screened by title and abstract.

Study selection was conducted in duplicate by two authors. Both authors independently reviewed all records by title and abstracts, and then full text. Title and abstract selection were conducted using Rayyan software. Differences in study selections were settled via consensus at each stage of the selection process.

8. Synthesis of Evidence Base

8.1 Evidence Base Pertaining to Efficacy, Effectiveness and Safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

8.1.1 PRISMA flow diagram

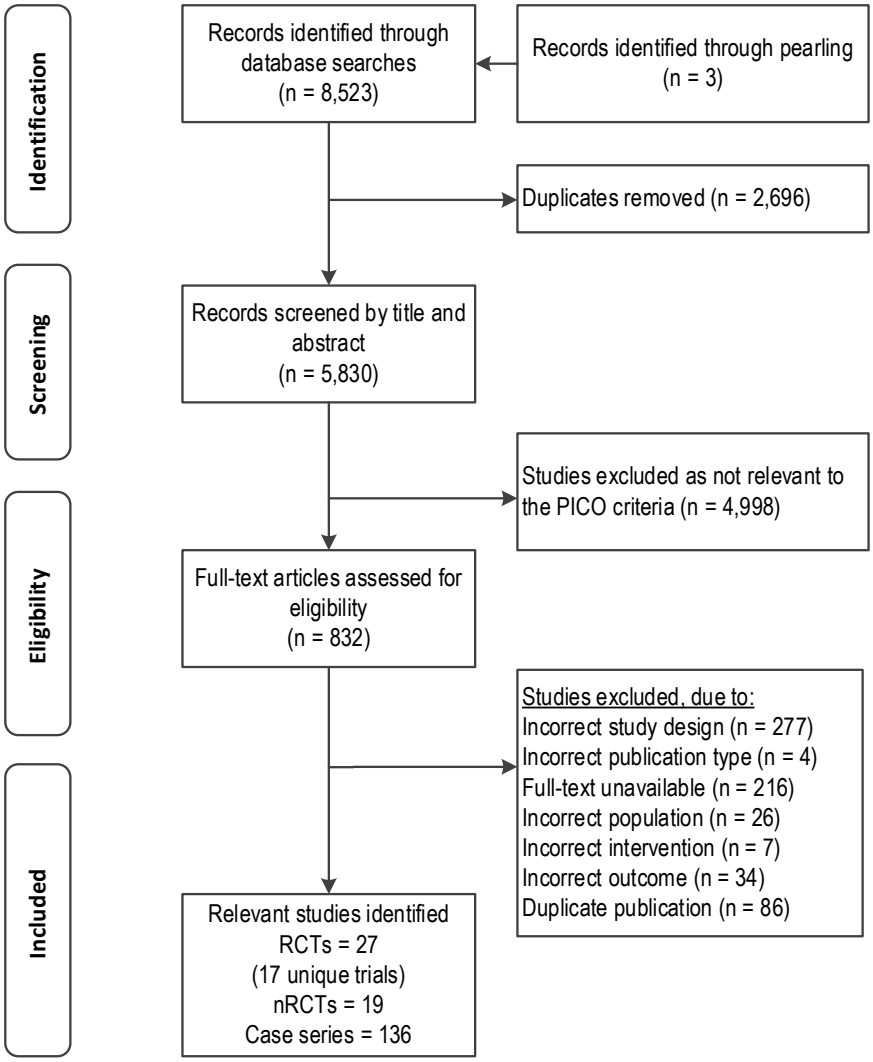
The results of the systematic literature searches are presented in **Figure 1Error! Reference source not found.**. The database searches and pearling of relevant studies yielded a total of 8,526 results. After removal of duplicates, 5,830 citations were reviewed by title and abstract, and of these, 832 were reviewed by full text. A total of 27 publications reporting on 17 unique RCTs, 19 nRCTs and 136 single-arm studies met the inclusion criteria for the clinical section of the scoping report.

In total, the searches identified 17 unique RCTs (from 27 publications) reporting on the clinical efficacy, effectiveness and safety of vertebroplasty and kyphoplasty, in addition to 19 non-randomised studies and 136 single-arm studies. “Unique” trials in this context refers to an individual study reported in one or more peer-reviewed articles. The included studies are as follows:

- **Efficacy/effectiveness compared to a sham procedure**
    - 4 unique RCTs compared a sham procedure to vertebroplasty
    - 8 unique RCTs compared non-surgical treatment to vertebroplasty
    - 5 unique RCTs compared non-surgical treatment to kyphoplasty

- **Safety**[1]
    - 10 nRCTs compared non-surgical treatment to kyphoplasty
    - 12 nRCTs compared non-surgical treatment to vertebroplasty
    - 136 case series investigated vertebroplasty and/or kyphoplasty

Figure 1 PRISMA flow chart for study inclusion



Abbreviations: **nRCT =** non-randomised controlled trial, **RCT =** randomised controlled trial.

[1] Three non-randomised comparative studies included both vertebroplasty and kyphoplasty compared to non-surgical treatment. Each comparison has been reported separately in this section, meaning studies were counted more than once. This is why the total number of studies reported here (n=22) does not match the PRISMA chart (n=19).

The characteristics of the trials included for the efficacy/effectiveness of PVP and PBK are summarised in **Table 18** and **Table 19**, respectively (Appendix B: Characteristics of Included Studies).

While no included RCTs were conducted wholly in Switzerland, one RCT had a study centre in Fribourg, Switzerland and the remainder were conducted in countries and settings broadly consistent with the Swiss context.[81] Of the included RCTs investigating PVP, most were conducted in European countries (the Netherlands, UK, Spain, Italy, France, Switzerland and Denmark (n=8). Others were conducted in Australia (n=3), the USA (n=2), China (n=2), and Iran (n=1). Four of the included PVP RCTs were single-centre and eight were multi-centre trials.

Of the included RCTs investigating kyphoplasty, three were conducted in China, one was conducted in eight centres in Germany, and the FREE trial was performed in eight European countries (Austria, Belgium, France, Germany, Italy, Sweden, the Netherlands, and the UK). Multinational trials on PVP were conducted across China and the USA (Yang et al. 2016), and across the USA, the UK and Australia (INVEST trial). Multinational collaborations offer the benefit of broader patient demographics.[82]

Sham-controlled trials of PVP included a total of 509 patients, and non-surgical treatment trials included 1,205 patients. The RCTs on kyphoplasty included 466 participants. Included RCTs ranged in sample size from 41 to 400 patients (median=220). Most PVP/PBK studies were conducted across multiple centres (n=12), with the number of collaborating centres ranging from 3 to 21. Almost half of the studies had a follow-up period of 12 months (n=10), with the length of follow-up ranging from post-operative to 36 months.

Patient indications included a diagnosis of osteoporosis with at least one painful fracture and pain severity reported according to visual analogue or numerical rating scale. It was a requirement that fracture be confirmed by X-ray, MRI or activity on a bone scan indicated by the presence of oedema or fracture line. Patients in most included studies were required to be refractory to medical treatment.

Clinical duration of vertebral fracture ranged from two days to one year. The majority of studies (n=14) reported on patients having clinical presence of vertebral fracture for less than eight weeks.

Pain and quality of life improvements are key outcomes of PVP and PBK. Because these are subjective patient-reported measures, adequate blinding of patients and outcome assessors is critical to ensure that effect estimates are unbiased. The included sham-controlled RCTs investigating PVP comprise a mix of single-, double- and un-blinded designs, however, the majority did not blind outcome assessors. Sham-procedure trials attempted to blind patients to the intervention in similar ways, typically by putting the patient under sedation, mixing cement in the room in order for the smell to permeate, and inserting a needle into the pedicle without injecting cement. In contrast, all of the PBK trials were controlled using non-surgical treatment, so blinding was not possible. A full investigation of risk of bias would be conducted in an HTA report, using the Cochrane Risk of Bias tool for RCTs version 2.0.[83]

Single-arm studies reporting safety outcomes consist of 49 investigating kyphoplasty, 65 investigating PVP, 21 investigating a combination of PVP and PBK, and one investigating sacroplasty. To minimise the risk of selection bias all included single-arm studies were prospective. Follow-up ranged from immediate post-operative to five years. The largest sample size was 564 patients.

Summaries of the outcomes reported for each intervention are described in **Table 10** and **Table 11**.

Table 10 Number of studies identified for the relevant outcomes, per study design – PVP

Outcome		Study design			
		Single arm	nRCT (vs non-surgical treatment)	RCT (vs non-surgical treatment)	RCT (vs sham procedure)
Pain	VAS	N/A	N/A	14	4
	NRS	N/A	N/A	-	4
Function	SOF-ADL	N/A	N/A	-	1
	DPQ	N/A	N/A	3	2
	RDQ	N/A	N/A	4	5
	ODI	N/A	N/A	4	-
	MMSE	N/A	N/A	1	-
	OPAQ	N/A	N/A	-	1
QoL	SF-12 / -36	N/A	N/A	3	1
	AQoL	N/A	N/A	-	2
	QUALEFFO	N/A	N/A	4	6
	EQ-5D	N/A	N/A	5	5
Analgesic consumption*		N/A	4	5	5
Safety	Serious adverse events	34	3	5	4
	Procedure-related mortality	22	2	6	-
	Subsequent/adjacent fractures (comparative only)	N/A	5	3	3
	Patient/physician exposure to radiation	5	-	-	-
	Other adverse events	87	16	13	5

*Analgesic consumption refers to any medication used for the sole purpose of relieving pain. This may include, but is not limited to, paracetamol, non-steroidal anti-inflammatory drugs, and opioids.

Abbreviations: **AE** = adverse events, **AQoL** = Assessment of Quality of Life, **DPQ** = Dallas Pain Questionnaire, **EQ-5D** = EuroQol 5-dimension scale, **MMSE** = mini-mental state examination, **N/A** = not applicable, **nRCT** = non-randomised controlled trial, **NRS** = numerical rating scale, **ODI** = Oswestry Disability Index, **OPAQ** = Osteoporosis Assessment Questionnaire, **QUALEFFO** = Quality of Life Questionnaire of the European Foundation for Osteoporosis, **RCT** = randomised controlled trial, **RDQ** = Roland-Morris Disability Questionnaire, **SF-12/-36** = Short Form-12/36, **SOF-ADL** = Study of Osteoporotic Fractures—Activities of Daily Living, **VAS** = visual analogue scale.

Table 11 Number of studies identified for the relevant outcomes, per study design – PBK

Outcome		Study design			
		Single arm	nRCT (vs non-surgical treatment)	RCT (vs non-surgical treatment)	RCT (vs sham procedure)
Pain	VAS	N/A	N/A	3	-
	BI	N/A	N/A	1	-
Function	RDQ	N/A	N/A	1	-
	ODI	N/A	N/A	1	-
QoL	SF-12 / -36	N/A	N/A	2	-
	EQ-5D	N/A	N/A	1	-
Analgesic consumption*		N/A	2	-	-
Safety	Serious adverse events	27	2	2	-
	Procedure-related mortality	17	1	-	-
	Adjacent fracture	N/A	3	-	-
	Exposure to radiation	1	-	-	-
	Other adverse events	61	8	1	-

*Analgesic consumption refers to any medication used for the sole purpose of relieving pain. This may include, but is not limited to, paracetamol, non-steroidal anti-inflammatory drugs, and opioids.

Abbreviations: **BI** = Barthel Index, **EQ-5D** = EuroQol 5-dimension scale, **N/A** = not applicable, **nRCT** = non-randomised controlled trial, **ODI** = Oswestry Disability Index, **RCT** = randomised controlled trial, **RDQ** = Roland-Morris Disability Questionnaire, **SF-12/-36** = Short Form-12/36, **VAS** = visual analogue scale.

Ongoing clinical trials may be considered as evidence where a large study on the PICO under assessment is due for completion before the end of the HTA. A list of identified ongoing clinical trials is presented in **Table 12Error! Reference source not found.**, including four RCTs on PVP compared to non-surgical treatment or sham procedure, and three non-randomised trials. Follow-up times range from 3 months to 24 months. None of the identified trials are likely to conclude in the near future and are therefore unlikely to be included in the clinical evaluation in the HTA report.

Table 12 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Expected completion date; Status
NCT01963039 (Vertos V)	Acute OVCF 180 participants	RCT	Vertebroplasty	Sham procedure	Pain with VAS up to 12 months	July 2018 Unknown
NCT03360383	Acute OVCF 400 participants	RCT	Vertebroplasty	Non-surgical treatment	Change in WHO classified pain status up to 12 months	June 2020 Not yet recruiting

NCT03617094	Acute (<10 days) vertebral fracture in patients aged >50 58 participants	RCT	Vertebroplasty	Non-surgical treatment	Difference in kyphotic angle at 3 months. Improvement in VAS pain up to 3 months	December 2020 Recruiting
NCT01677806	Acute (clinical onset ＜ 6 weeks) OVCF in patients aged > 50 140 participants	RCT	Vertebroplasty	Non-surgical treatment	Pain at 1 month. Function, quality of life, and incident fractures at 1, 3, 6 and 12 months	December 2014 Last update September 2014 Status unknown
ChiCTR1800016493	OVCF of the thoracolumbar spine 900 participants	Non-RCT	Vertebroplasty	Kyphoplasty Physical therapy and TCM	Back pain incidence up to 2 years. VAS & ODI up to 6 months	November 2021 Recruiting
NCT03330340	Osteoporosis 106 participants	Non-RCT	Vertebroplasty	Non-surgical treatment	Incidence of vertebral re-fracture up to 12 months	December 2019 Not yet recruiting
NCT03692143	Women with OVCF 90 participants	Non-RCT	Vertebroplasty without teriparatide	Vertebroplasty with teriparatide. Injection of teriparatide daily	QoL up to 2 years with SF-36 up to 24 months	December 2030 Active, not recruiting

Abbreviations: **NCT** = ClinicalTrials.gov identifier, **ODI =** Oswestry Disability Index, **OVCF** = osteoporotic vertebral compression fracture, **QoL** = Quality of Life, **SF-36** = 36-item Short Form general health survey, **TCM** = traditional Chinese medicine, **VAS** = visual analogue scale, **WHO** = World Health Organisation.

8.2 Evidence Base Pertaining to Costs, Budget Impact and Cost-Effectiveness

In all, 67 potentially relevant studies were screened by full-text. Recently published HTAs were screened for reports including full economic evaluations. Economic studies published before 2009 were excluded due to a lack of clinical evidence available to inform economic evaluations conducted before this time. Any study reporting cost, cost-effectiveness or budget impact data was retrieved, however, this review focused on full economic evaluations and their applicability to a cost-effectiveness analysis in the Swiss context.

In summary, six full economic evaluations and one systematic review of economic evaluations of PVP and/or PBK in OVCFs were identified.[84-90] Published economic evaluations included both trial-based (n=2)[85 86] and modelled (n=4)[87-90] analyses. One of the model-based evaluations was extracted from a published HTA report.[87] The systematic review published by Borgström et al.[84] included five economic evaluations, all of which were captured in this literature search.[85-89] An economic evaluation published since the time of the systematic review was also captured.[90]

It is noted that a 2011 report conducted on behalf of the Medical Services Advisory Committee (MSAC) in Australia did not perform a modelled economic evaluation owing to an evidence base that did not support such an analysis.[12] The appropriateness of a full economic evaluation should be guided by the findings of the safety and effectiveness review. The systematic review published by Borgström et al.[84] highlights the following as key drivers of variations in cost-effectiveness outcomes across the five evaluations available at the time:

- Time horizon
- Quality of life effect of treatment
- Offset time of the treatment effect
- Reduced number of bed days associated with procedures
- Mortality benefit associated with treatment

Table 13 and **Table 14** show how these points relate to the six full economic evaluations identified. Separate summary tables are provided for trial-based and model-based evaluations owing to inherent differences in the nature of each approach. Notably, within-trial analyses are restricted to the length of follow up of the trials themselves, while model-based evaluations are able to take a longer horizon. Restricted time horizons are a potentially limiting factor, failing to account for longer-term differences in costs and outcomes. Conversely, model-based approaches introduce complexities such as the need to make assumptions, to extrapolate, and to source data externally.

Within-trial

The within-trial analyses presented by Klazen et al.[86] and Fritzell et al.[85] were performed alongside the VERTOS II and the FREE trials, respectively. Fritzell et al.[85] restricted their evaluation to the Swedish subset of patients from the FREE trial. **Table 13** provides an overview of these evaluations.

Table 13 Overview of within-trial economic evaluations

	Klazen et al. (2010)[86]	**Fritzell et al. (2011)[85]**
Trial name	VERTOS II	Swedish patients in the FREE trial
Country	Netherlands and Belgium*	Sweden
Comparators	PVP, NSM	PBK, NSM
Costing year	2008	2008
Time horizon	1 year	2 years
Perspective	Healthcare	Healthcare and Societal
Patient characteristics	Age: 75.2 (PVP) vs. 75.4 (NSM) Gender: 69% female (PVP) vs. 69% female (NSM)	Age: 72 (PBK) vs. 75 (NSM) Gender: 71% female (PVP) vs. 78% female (NSM)
Outcome of economic evaluation	Cost per pain-free day gained** Cost per QALY gained	Cost per QALY gained
Tool used to measure QoL	EQ-5D	EQ-5D

* Five teaching hospitals in the Netherlands and one in Belgium.
** A pain-free day was defined as a day with a VAS score of ≤3.

Source: Adapted in part from Borgström et al.[84] (Table 1 p.1241).
Abbreviations: EQ-5D = EuroQol-5D, **NSM** = non-surgical management, **QALY** = quality-adjusted life year, **PBK** = percutaneous balloon kyphoplasty, **PVP** = percutaneous vertebroplasty.

Model-based

Ström et al.[88] undertook a cost-utility analysis of PBK versus non-surgical management (NSM) from a UK healthcare perspective. The Markov model they developed has since been adopted by Takahashi et al. and Svedbom et al.[89 90] The HTA report published by Stevenson et al.[87] employed a Markov model of similar design to assess the cost-effectiveness of PVP, PBK and operational local anaesthesia (OPLA) compared to NSM from a UK healthcare perspective. **Table 14** provides an overview of these evaluations.

Table 14 Overview of the model-based economic evaluations

	Ström et al. (2010)[88]	Svedbom et al. (2013)[89]	Stevenson et al. (2014)[87]	Takahashi et al. (2019)[90]
Characteristics:				
Country	UK	UK	UK	Japan
Comparators	PBK, NSM	PBK, PVP, NSM	PBK, PVP, NSM, OPLA	PBK, NSM
Costing year	2008	2009	2010-11	2018
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime
Perspective	Healthcare	Healthcare	Healthcare	Unclear*
Base case patient characteristics	70-year-old, 77% female, T-score -2.5	70-year old female, T-score of -3.	70-year old female, T-score of -3	No 'base patient' given. *Characteristics of included cohorts:* Age: 78.3 (PBK) vs. 77.7 (NSM) Gender: 87% female (PBK) vs. 87% female (NSM).
Outcome	Cost per QALY gained	Cost per QALY gained	Cost per QALY gained	Cost per QALY gained
Quality of Life Data:				
Source	Initial 12 months of the FREE trial.	Complete 24 months of the FREE trial and the VERTOS II trial**	Network meta-analysis of studies reporting VAS scores. Studies directly reporting EQ-5D outcomes considered as an alternate source.	Two distinct cohorts, treated at distinct time points in the Osaka area, Japan. Patients matched based on propensity score – 71 pairs were selected.
Tool used to measure QoL	EQ-5D	EQ-5D	Two alternatives were considered: • VAS scores mapped to EQ-5D, or • Direct EQ-5D results	SF-6D
Duration of any observed difference in quality of life	1 year based on trial data. Thereafter, difference assumed to linearly approach zero over a 2-year period.	2 years based on trial data. Thereafter, difference assumed to approach zero over a 1-year period	Observed VAS scores at 1 month (PVP, PBK and OPLA) and 3 months (NSM) assumed stable up to 2 years. Thereafter, difference assumed to approach zero over an additional 1-year period	3 years
Mortality Assumptions:				
Increased mortality risk due to fracture	Yes, up to 5 years post VCF. Derived from Swedish data.	Yes, following the method taken by Ström et al.[88]	Yes. Increased risk assumed up to 5 years post VCF. Increased risk thereafter approaches zero over an additional 5-year	Doesn't seem so. Mortality data sourced from Japanese abridged life tables

			period (base case)	
Mortality benefit associated with vertebral augmentation procedure	No	Yes. Mortality derived from Swedish data was assumed to be reflective of mortality in NSM arm given very few PBKs and PVPs are conducted in Sweden. 4-year mortality hazard ratios for PBK and PVP compared to NSM were applied.	Yes. Two foundational analyses rather than a base case were presented – with and without a mortality benefit. Where a mortality benefit was assumed, it was assumed to last for 5 years. In the six scenario analyses, the 3 alternate assumptions regarding the mortality benefit of augmentation procedures compared to NSM were: • PBK > PVP > NSM, • PBK = PVP > NSM, and • PBK = PVP = NSM	Unclear; likely yes***
Risk of re-fracture:				
Re-fracture rate considered	Yes, additional VCFs	Yes, additional VCFs	Yes. One subsequent vertebral and one subsequent hip fracture were permitted per patient over the model.	Yes, additional VCFs
Re-fracture rate different between treatment arms	No	Not in the base case. Sensitivity analysis tested this assumption	No	Not specified
Other				
Reduced number of bed days	Yes, assumed six fewer bed days for PBK compared to NSM	Yes. Assumed that both PBK and PVP are associated with six fewer bed days compared to NSM (9 vs 15 days)	Yes. Although noted this is uncertain. *Base case (days):* PVP 6.2, PBK 5.1, and NSM 9.5	Data tabulated although unclear if this is incorporated into the modelled analysis (15.2 vs 66.2 days)
Adverse events	No	No	No (base case). Sensitivity analysis only	No

***** Based on costs outlined in Table 1, it appears to be a healthcare perspective however p.E301 refers to the difference in 'societal' costs.
** PVP vs. NSM results (from VERTOS II) were normalised to the NSM-arm results from the FREE trial (PBK vs. NSM) and extrapolated into the second year by assuming the same proportional benefit in year 2 relative to year 1 as observed for PBK in the FREE trial.
*** A study reporting risk of mortality to be 44% lower in PBK cohort than NSM cohort is referred to in the body of the text, however, how this figure is incorporated into the base case analysis is not clarified. Sensitivity analyses were performed with and without the base case mortality benefit of PBK compared with NSM. Therefore, it can be assumed some benefit is incorporated into the base case.
Source: Adapted in part from Borgström et al.[84] (Table 1 p.1241).
Abbreviations: EQ-5D = EuroQol-5D, **NSM** = non-surgical management, **OPLA** = operational local anaesthesia, **QALY** = quality-adjusted life year, **VAS** = visual analogue scale, **VCF** = vertebral compression fracture, **PBK** = percutaneous balloon kyphoplasty, **PVP** = percutaneous vertebroplasty.

The modelled evaluations all took a lifetime horizon. In order to extrapolate clinical observations over the lifetime of the patient, assumptions were made regarding how any observed differences in QoL between treatment arms were modelled beyond the follow-up period. Data sources and assumptions are summarised in **Table 14**.

The Ström model[88] allows for additional vertebral fractures to occur, while the Stevenson model[87] allows for subsequent hip fractures in addition to vertebral fractures. In the evaluations conducted, subsequent fractures were considered to be a result of the underlying disease process. Re-fracture rates were assumed to be consistent across treatment arms in base case analyses.

Notably, serious adverse events were not considered in any of the model base cases. They were omitted entirely from three models either without discussion, or said to be due to a lack of available evidence or the good safety profile (BKP).[88-90] Adverse events were considered in the sensitivity analyses performed by Stevenson et al.[87]

Increased mortality due to fracture was generally incorporated. No differential treatment effect on mortality was considered by Ström et al,[88] whereas Svedbom et al.[89] assumed vertebral augmentation is associated with reduced mortality up to four years post fracture. Stevenson et al.[87] presented two foundational analyses instead of a single base case, owing to an inability to conclude whether treatment choice has any impact on mortality risk. Poor reporting by Takahashi et al.[90] renders it difficult to clarify the source and use of some input variables, however, a mortality benefit for PBK was likely incorporated into the base case.

Stevenson et al.[87] reported an evaluation with extensive sensitivity and scenario analyses. Uncertainty in the underlying evidence is reflected in the results, with the authors noting that insufficient evidence prevented conclusions being drawn. Key areas of uncertainty were the differential effect of treatment on mortality and the length of stay for PVP and PBK procedures.[87]

Applicability of the economic analyses to the Swiss context

Three of the four model-based evaluations were conducted in the UK,[87-89] and one was conducted in Japan.[90] The assumptions and some input data incorporated into these evaluations may be generalisable to the Swiss context, however, inputs should be updated to reflect Swiss-specific values where possible, particularly in regard to cost inputs. One of the trial-based evaluations was performed in Sweden and the other in the Netherlands.[85 86]

It was previously noted (Section 3.3: Conduct of the Procedures) that in Switzerland, PVP is most commonly performed in a day surgery suite, while PBK is performed as an inpatient procedure under general anaesthetic. An assumption underlying all model-based evaluations is that surgical management with either PBK or PVP is associated with fewer hospital bed days than non-surgical management. Stevenson et al.[87] emphasised the considerable uncertainty surrounding the length-of-stay input data, implying that inputs may

not accurately reflect clinical practice if PVP and/or PBK are performed as day procedures. The nature of the delivery of these interventions in Switzerland should be considered when modelling the length-of-stay data in any subsequent analysis. Any benefit incorporated should be feasible within the context of delivery in Switzerland.

The systematic review by Borgström et al.[84] concluded that cost-effectiveness outcomes were dependent upon model input details, recommending that additional evidence be produced to reduce the uncertainty in input data used in any subsequent economic evaluation. Clinical efficacy/effectiveness and the possible effect on mortality were considered to be the main areas of uncertainty and the need for longer-term clinical outcome evidence was highlighted.[84]

The studies examined in the Borgström et al.[84] review were published in 2014 or earlier[84]. Since this time, new trials reporting safety and effectiveness data for both PVP (six RCTs) and PBK (three RCTs) have been published, which would be included for review in a full HTA (See Appendix, **Table 18** and **Table 19**). Length of follow-up in these more recent trials generally extends from 6-12 months, so longer-term clinical outcome data may remain elusive. Nonetheless, it is anticipated that findings from these trials may reduce modelling uncertainties surrounding clinical effectiveness inputs.

Were a de novo economic evaluation to be performed, it is likely to be a model-based evaluation employing a universal model structure across PBK and PVP. Historically, model-based evaluations have been performed to analyse the cost-effectiveness of PBK and/or PVP compared to non-surgical treatment. An updated model is suggested as the best approach for any future HTA. The current economic literature carries a high level of uncertainty owing to limitations in the evidence base. Since the majority of these economic evaluations were published more recent data has become available, which may reduce some of the clinical uncertainties. Discrepancies between the modelled scenarios and clinical practice in Switzerland, particularly regarding the mode of delivery of PVP, mean that currently available economic results may not accurately reflect the Swiss clinical context. The decision to conduct a de novo economic evaluation will be guided by the findings of the safety and effectiveness review.

8.3 Evidence Base Pertaining to Legal, Social and Ethical Issues

8.3.1 Legal Issues

There are limited legal issues relating to the potential disinvestment of PVP and PBK. Authors from Germany and the USA have published two literature reviews[91 92] and one commentary[93] identifying legal issues related to PVP/PBK. Key issues were the importance of obtaining informed consent before the procedure, including the legal principles of informing the patient of the risks of the procedure, and that of disclosing to the patient the majority approach. Another issue concerns conflicting clinical practice guidelines, namely those of the American College of Radiology (ACR) and the American Academy of Orthopaedic Surgeons (AAOS), especially as such guidelines can theoretically be used in court as evidence of appropriate standard of care.

8.3.2 Social Issues / Patient Perspectives

Four studies by various authors from Germany and the USA identified patient perspectives or social issues concerning the intervention. These include one case control study of OVCF patients undergoing kyphoplasty compared with historically matched OVCF patients treated conservatively,[94] one phone survey,[95] one retrospective chart review,[96] and a review article.[91] Key issues identified include the importance of patient information and informed consultation before the procedure, the effect of a patient follow-up and education service on reducing re-fractures, patient perception of kyphoplasty post-surgery and the likelihood of agreeing to a repeat procedure, and social drift disadvantaging post-OVCF care in both PVP and conservatively managed patients.

8.3.3 Ethical Issues

Six studies with authors from Switzerland, Greece, Canada, Australia and the USA identified ethical issues about the intervention. One cohort study on the Swiss population emphasised the high variation of PVP and PBK procedures amongst different regions in Switzerland and the possibility that this may represent over-treatment in the high-use areas, which is an ethical concern.[1] The five other papers—editorials, commentaries, reviews and umbrella reviews—described the ongoing debate on the efficacy of PVP after two sham-controlled trials found limited benefits.[55 97-100] The papers outline the clinical experience that conflicts with the findings of recent sham-controlled trials, discuss the implications of basing patient management on the findings of these trials, and call for the continued evaluation of PVP. An earlier editorial questioned the ethics of conducting double-blind RCTs on PVP, stating that non-surgical treatments had, by definition, already failed, thus patients randomised to the control would be disadvantaged.[101]

8.4 Evidence Base Pertaining to Organisational Issues

Two studies, with authors from Switzerland, Greece, and the USA, identified issues around organisational factors pertaining to the intervention.

A population-based study[1], likely to be the most relevant to the dis-imbursement of PVP and/or PBK in Switzerland, utilised discharge data from all Swiss hospitals and Swiss census data over a two-year period. The other study, a review article, updated an earlier meta-analysis.[14].

The Swiss study reported ten-fold variation in rates of PVP and PBK performed across Swiss Hospital Service Areas. The authors inferred that the variation was most likely attributable to differing practices of physicians in response to confusion and controversy regarding the effectiveness of the two procedures.

9. Feasibility HTA

This scoping review has identified a moderately sized evidence base evaluating PVP in comparison to sham procedure and non-surgical treatment. There is sufficient evidence to conduct a meta-analysis of the critical efficacy/effectiveness outcomes, and a subgroup analysis related to fracture age.

In contrast, there is less evidence for PBK. All of the available RCTs are active-controlled trials comparing PBK to non-surgical treatment. There appears to be sufficient evidence to perform meta-analysis on the primary outcomes of pain and quality of life, but data for function are limited to individual studies. A review of the available evidence for PBK in the context of the current limitations on the reimbursement of the procedure in Switzerland, will inform whether it should continue to be reimbursed or not.

Limited evidence was identified for organisational, legal, social and ethical issues. Inpatient care to treat acute OVCFs may increase if reimbursement were to cease. The organisational impacts of such a decision should be investigated via consultation with affected hospitals. The inclusion of patient and social views will be collected to inform the FOPH decision-making process.

We conclude that there is sufficient evidence to undertake a full HTA on the efficacy, effectiveness and safety of PVP and PBK for painful OVCFs. A key focus of the PVP review should be the timing of the procedure in the life of the fracture, to determine whether the service should be limited to specific OVCF-patient subgroups. The HTA should also present a bespoke economic analysis, and review patient and social perspectives to ensure the evidence review is fair and accounts for patient and physician perspectives.

10. Outlook

10.1 Clinical Evaluation

The clinical evaluation will include a meta-analysis of published RCTs comparing PVP or PBK against sham procedure or conservative management. Where sufficient data is available, subgroup analysis will include:

- Fracture age: acute fracture (defined as less than eight weeks duration) compared to non-acute fracture groups (defined as greater than eight weeks duration).[13 23]

10.2 Economic Evaluation

If an economic evaluation were to proceed, a de novo evaluation would be required because the existing economic models identified in the literature are obsolete and do not include the most recent clinical data on the efficacy/effectiveness of PVP or PBK. Literature is available to inform the structure of a model-based economic evaluation; however, it is advisable that the safety and effectiveness evidence base be re-assessed to potentially increase certainty around model assumptions and to include QoL treatment effect.

A classification matrix covering outcomes of clinical safety and effectiveness will be used to determine the type of economic evaluation to be conducted (**Table 15**Error! Reference source not found.).

Table 15 Classification of economic evaluation types

		Comparative effectiveness			
Comparative safety		**Inferior**	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
	Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
	Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
	Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
	Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

Abbreviations: **CEA** = cost-effectiveness analysis; **CMA** = cost-minimisation analysis; **CUA** = cost-utility analysis
Notes: **?** = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis; **a** Uncertainty covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations; **b** An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

Inputs for the potential economic evaluation will be identified through a range of sources, including targeted literature searches of biomedical databases, existing HTA reports and government databases. Costs associated with PVP, PBK and non-surgical treatment would 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 (e.g. analgesics). Clinical expert advice will be sought if information cannot be identified through published sources. Key assumptions, particularly those sought from clinical advice, would be investigated via sensitivity analysis.

10.3 Social, Legal, Ethical, Organisational Issues

Patient and carer views are important to the evaluation of patient and social issues related to the use of PVP and PBK. Where relevant data can not be obtained through a review of the literature, input from targeted stakeholder groups would be obtained through collaboration with the FOPH. Input from patients and physicians would be gathered by a targeted stakeholder engagement with patient and physician organisations during. Additional grey literature databases able to be searched for the full HTA are listed in Appendix A.

11. References

1. Scheuter C, Wertli MM, Haynes AG, et al. Unwarranted regional variation in vertebroplasty and kyphoplasty in Switzerland: A population-based small area variation analysis. *PLoS One* 2018;13(12):e0208578.
2. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2016;388(10052):1408-16.
3. Firanescu CE, de Vries J, Lodder P, et al. Percutaneous Vertebroplasty is no Risk Factor for New Vertebral Fractures and Protects Against Further Height Loss (VERTOS IV). *Cardiovasc Intervent Radiol* 2019
4. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *New England Journal of Medicine* 2009;361(6):569-79.
5. Wang B, Guo H, Yuan L, et al. A prospective randomized controlled study comparing the pain relief in patients with osteoporotic vertebral compression fractures with the use of vertebroplasty or facet blocking. *Eur Spine J* 2016;25(11):3486-94.
6. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous Vertebroplasty Versus Conservative Treatment in Aged Patients With Acute Osteoporotic Vertebral Compression Fractures: A Prospective Randomized Controlled Clinical Study. *Spine (Phila Pa 1976)* 2016;41(8):653-60.
7. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;361(6):557-68.
8. Blasco J, Martinez-Ferrer A, Macho J, et al. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. *J Bone Miner Res* 2012;27(5):1159-66.
9. American College of Radiology. ACR–ASNR–ASSR–SIR–SNIS practice parameter for the performance of vertebral augmentation 2018. Available from: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/VerebralAug.pdf?la=en, Accessed 10 August 2019.
10. McGuire R. AAOS Clinical Practice Guideline: the Treatment of Symptomatic Osteoporotic Spinal Compression Fractures. *J Am Acad Orthop Surg* 2011;19(3):183-4.
11. National Institute of Health and Care Excellence (NICE). Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures London2016. Available from: https://www.nice.org.uk/guidance/ta279/chapter/1-Guidance, Accessed 8 May 2019.
12. Medical Services Advisory Committee. 27.1 Review of Kyphoplasty for the Treatment of Vertebral Compression Fracture and Review of Interim Funded Service: Vertebroplasty for the Treatment of Vertebral Compression Fracture 2011. Available from: http://webarchive.nla.gov.au/gov/20160615053438/http://www.msac.gov.au/internet/msac/publishing.nsf/Content/27.1-public.
13. Das Eidgenössische Departement des Innern(EDI). Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung: KLV **2019**. Available from: https://www.admin.ch/opc/de/classified-compilation/19950275/index.html, Accessed 20 April 2019.
14. Papanastassiou ID, Filis A, Gerochristou MA, et al. Controversial issues in kyphoplasty and vertebroplasty in osteoporotic vertebral fractures. *Biomed Res Int* 2014;2014:934206.
15. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *The American Journal of Medicine* 1993;94(6):646-50.
16. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 2013;8:136.
17. Harrop JS, Prpa B, Reinhardt MK, et al. Primary and secondary osteoporosis' incidence of subsequent vertebral compression fractures after kyphoplasty. *Spine (Phila Pa 1976)* 2004;29(19):2120-5.

18. Phuan-Udom R, Lektrakul N, Katchamart W. The association between 10-year fracture risk by FRAX and osteoporotic fractures with disease activity in patients with rheumatoid arthritis. *Clinical rheumatology* 2018;37(10):2603-10.

19. Keller TS, Harrison DE, Colloca CJ, et al. Prediction of osteoporotic spinal deformity. *Spine (Phila Pa 1976)* 2003;28(5):455-62.

20. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *Jama* 2001;285(3):320-3.

21. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev* 2018;11:Cd006349.

22. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. *Bmj* 2018;361:k1551.

23. Rousing R, Andersen MO, Jespersen SM, et al. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. *Spine (Phila Pa 1976)* 2009;34(13):1349-54.

24. Swiss Society of Spinal Surgery. Schweizerische Gesellschaft für Spinale Chirurgie 2004. Available from: https://www.bag.admin.ch/dam/bag/de/dokumente/kuv-leistungen/referenzdokumente-klv-anhang-1/01.3-richtlinien-vom-23.09.2004-betreffend-ballon-kyphoplastie-zur-behandlung-von-wirbelkoerperfrakturen.pdf.download.pdf/01.3%20Richtlinien%20der%20Schweizerische%20Gesellschaft%20f%C3%BCr%20Spinale%20Chirurgie%20vom%2023.09.2004%20betreffend%20Ballon-Kyphoplastie%20zur%20Behandlung%20von%20Wirbelk%C3%B6rperfrakturen%20(in%20englisch).pdf, Accessed 20 April 2019.

25. Firanescu C, Lohle PN, de Vries J, et al. A randomised sham controlled trial of vertebroplasty for painful acute osteoporotic vertebral fractures (VERTOS IV). *Trials* 2011;12:93.

26. Jin C, Xu G, Weng D, et al. Impact of Magnetic Resonance Imaging on Treatment-Related Decision Making for Osteoporotic Vertebral Compression Fracture: A Prospective Randomized Trial. *Med Sci Monit* 2018;24:50-57.

27. Kao F-C, Hsu Y-C, Liu P-H, et al. Osteoporotic sacral insufficiency fracture: An easily neglected disease in elderly patients. *Medicine* 2017;96(51):e9100-e00.

28. Reitman C, Mathis K, Heggeness MH. CHAPTER 65 - An Orthopedic Perspective of Osteoporosis. In: Marcus R, Feldman D, Nelson DA, et al., eds. Osteoporosis (Third Edition). San Diego: Academic Press 2008:1555-73.

29. Yadollahi M, Paydar S, Ghaem H, et al. Epidemiology of Cervical Spine Fractures. *Trauma monthly* 2016;21(3):e33608-e08.

30. Bostrom MPG, Lane JM. Future Directions: Augmentation of Osteoporotic Vertebral Bodies. *Spine* 1997;22(24):38S-42S.

31. Kanterewicz E, Puigoriol E, Rodriguez Cros JR, et al. Prevalent vertebral fractures and minor vertebral deformities analyzed by vertebral fracture assessment (VFA) increases the risk of incident fractures in postmenopausal women: the FRODOS study. *Osteoporos Int* 2019

32. Melton LJ, 3rd. Epidemiology of spinal osteoporosis. *Spine (Phila Pa 1976)* 1997;22(24 Suppl):2s-11s.

33. McCarthy J, Davis A. Diagnosis and Management of Vertebral Compression Fractures. *Am Fam Physician* 2016;94(1):44-50.

34. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015;156(6):1003-07.

35. Riggs BL, Melton LJ, 3rd. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995;17(5 Suppl):505s-11s.

36. Bouza C, Lopez-Cuadrado T, Almendro N, et al. Safety of balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures in Europe: a meta-analysis of randomized controlled trials. *Eur Spine J* 2015;24(4):715-23.

37. Hall SE, Criddle RA, Comito TL, et al. A Case–Control Study of Quality of Life and Functional Impairment in Women with Long–Standing Vertebral Osteoporotic Fracture. *Osteoporosis International* 1999;9(6):508-15.

38. Lippuner K, Johansson H, Kanis JA, et al. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. *Osteoporos Int* 2009;20(7):1131-40.

39. Svedbom A, Ivergård M, Hernlund E, et al. Epidemiology and economic burden of osteoporosis in Switzerland. *Archives of Osteoporosis* 2014;9(1):187.

40. Liu Q, Cao J, Kong JJ. Clinical effect of balloon kyphoplasty in elderly patients with multiple osteoporotic vertebral fracture. *Nigerian journal of clinical practice* 2019;22(3):289-92.

41. Li Y, Zhu J, Xie C. A comparative study of percutaneous kyphoplasty and conservative therapy on vertebral osteoporotic compression fractures in elderly patients. *International Journal of Clinical and Experimental Medicine* 2017;10(5):8139-45.

42. Wang H, Sribastav SS, Ye F, et al. Comparison of Percutaneous Vertebroplasty and Balloon Kyphoplasty for the Treatment of Single Level Vertebral Compression Fractures: A Meta-analysis of the Literature. *Pain physician* 2015;18(3):209-22.

43. Gu CN, Brinjikji W, Evans AJ, et al. Outcomes of vertebroplasty compared with kyphoplasty: a systematic review and meta-analysis. *Journal of neurointerventional surgery* 2016;8(6):636-42.

44. Mathis JM, Ortiz AO, Zoarski GH. Vertebroplasty versus kyphoplasty: a comparison and contrast. *AJNR Am J Neuroradiol* 2004;25(5):840-5.

45. Nussbaum DA, Gailloud P, Murphy K. A Review of Complications Associated with Vertebroplasty and Kyphoplasty as Reported to the Food and Drug Administration Medical Device Related Web Site. *Journal of Vascular and Interventional Radiology* 2004;15(11):1185-92.

46. Hubschle L, Borgstrom F, Olafsson G, et al. Real-life results of balloon kyphoplasty for vertebral compression fractures from the SWISSspine registry. *Spine J* 2014;14(9):2063-77.

47. Schupfner R, Stoevelaar HJ, Blattert T, et al. Treatment of Osteoporotic Vertebral Compression Fractures: Applicability of Appropriateness Criteria in Clinical Practice. *Pain physician* 2016;19(1):E113-20.

48. Benneker LM, Hoppe S. Percutaneous cement augmentation techniques for osteoporotic spinal fractures. *European Journal of Trauma and Emergency Surgery* 2013;39(5):445-53.

49. Röllinghoff M, Zarghooni K, Schlüter-Brust K, et al. Indications and contraindications for vertebroplasty and kyphoplasty. *Archives of Orthopaedic and Trauma Surgery* 2010;130(6):765-74.

50. SASIS AG. Datenbank der santésuisse 2019. Available from: https://www.sasis.ch/, Accessed 9 May 2019.

51. SwissDRG AG. Stationnaire Tarifsysteme Datenbank.: Schweizerische Spitäler, 2019.

52. Scottish Intercollegiate Guidelines Network (SIGN). Control of Pain in Adults with Cancer: A national clinical guideline. SIGN 106. Edinburgh: SIGN, 2010.

53. Canadian Agency for Drugs and Technologies in Helath (CADTH). Balloon Kyphoplasty for the Treatment of Vertebral Compression Fractures: A Review of the Guidelines and Clinical and Cost-Effectiveness 2008. Available from: https://www.cadth.ca/balloon-kyphoplasty-treatment-vertebral-compression-fractures-adults-clinical-and-cost-effectiveness, Accessed 10 May 2019.

54. Eckel TS, Olan W. Vertebroplasty and Vertebral Augmentation Techniques. *Techniques in Vascular and Interventional Radiology* 2009;12(1):44-50.

55. Lamy O, Uebelhart B, Aubry-Rozier B. Risks and benefits of percutaneous vertebroplasty or kyphoplasty in the management of osteoporotic vertebral fractures. *Osteoporos Int* 2014;25(3):807-19.

56. Vogl TJ, Pflugmacher R, Hierholzer J, et al. Cement directed kyphoplasty reduces cement leakage as compared with vertebroplasty: results of a controlled, randomized trial. *Spine (Phila Pa 1976)* 2013;38(20):1730-6.

57. Zhang H, Xu C, Zhang T, et al. Does percutaneous vertebroplasty or balloon kyphoplasty for osteoporotic vertebral compression fractures increase the incidence of new vertebral fractures? A meta-analysis. . *Pain physician* 2017;20(1):E13-28.

58. ISPM and Obsan. Schweizer Atlas der Gesundheitsversorgung - Vertebroplastik Bern: Schweizer Akutspitälern; 2017. Available from: http://versorgungsatlas.ch/index.php/de/VERT/, Accessed 6 May 2019.

59. ISPM and Osban. Schweizer Atlas der Gesundheitsversorgung - Kyphoplastik Bern: Schweizer Akutspitälern; 2017. Available from: http://versorgungsatlas.ch/index.php/de/KYPH-2/, Accessed 6 May 2019.

60. Tsoumakidou G, Too CW, Koch G, et al. CIRSE Guidelines on Percutaneous Vertebral Augmentation. *Cardiovasc Intervent Radiol* 2017;40(3):331-42.

61. Esses SI, McGuire R, Jenkins J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the treatment of osteoporotic spinal compression fractures. *J Bone Joint Surg Am* 2011;93(20):1934-6.

62. Megale RZ, Pollack A, Britt H, et al. Management of vertebral compression fracture in general practice: BEACH program. *PloS one* 2017;12(5):e0176351-e51.

63. Prather H, Hunt D, Watson JO, et al. Conservative care for patients with osteoporotic vertebral compression fractures. *Phys Med Rehabil Clin N Am* 2007;18(3):577-91, xi.

64. Sinaki M, Itoi E, Wahner HW, et al. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. *Bone* 2002;30(6):836-41.

65. Zuo X-H, Zhu X-P, Bao H-G, et al. Network meta-analysis of percutaneous vertebroplasty, percutaneous kyphoplasty, nerve block, and conservative treatment for nonsurgery options of acute/subacute and chronic osteoporotic vertebral compression fractures (OVCFs) in short-term and long-term effects. *Medicine* 2018;97(29):e11544-e44.

66. Chandler G, Dalley G, Hemmer Jr J, et al. Gray ramus communicans nerve block: novel treatment approach for painful osteoporotic vertebral compression fracture. *Southern medical journal* 2001;94(4):387-93.

67. Pehora C, Pearson AM, Kaushal A, et al. Dexamethasone as an adjuvant to peripheral nerve block. *The Cochrane database of systematic reviews* 2017;11(11):CD011770-CD70.

68. Chakravarthy K, Richter H, Christo PJ, et al. Spinal Cord Stimulation for Treating Chronic Pain: Reviewing Preclinical and Clinical Data on Paresthesia-Free High-Frequency Therapy. *Neuromodulation* 2018;21(1):10-18.

69. Pang D. Current experience of spinal neuromodulation in chronic pain: Is there a role in children and young people? *Eur J Paediatr Neurol* 2017;21(1):56-66.

70. Bell J, Blacker N, Edwards S, et al. Osteoporosis Pharmacological prevention and management in older people. *Australian Family Physician* 2012;41:110-18.

71. Black DM, Bauer DC, Schwartz AV, et al. Continuing bisphosphonate treatment for osteoporosis--for whom and for how long? *N Engl J Med* 2012;366(22):2051-3.

72. Gambacciani M, Levancini M. Management of postmenopausal osteoporosis and the prevention of fractures. *Panminerva Med* 2014;56(2):115-31.

73. Chandra RV, Meyers PM, Hirsch JA, et al. Vertebral augmentation: report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery. *Journal of NeuroInterventional Surgery* 2014;6(1):7.

74. ICH Expert Working Group. Structure and content of clinical study reports E3: International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, **1995**.

75. Trout AT, Kallmes DF, Kaufmann TJ. New fractures after vertebroplasty: adjacent fractures occur significantly sooner. *AJNR American journal of neuroradiology* 2006;27(1):217-23.

76. Copay AG, Glassman SD, Subach BR, et al. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study

questionnaire Short Form 36, and pain scales. *The spine journal : official journal of the North American Spine Society* 2008;8(6):968-74.

77. Chandra RV, Meyers PM, Hirsch JA, et al. Vertebral augmentation: report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery. *J Neurointerv Surg* 2014;6(1):7-15.

78. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33(1):90-4.

79. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2005;14(6):1523-32.

80. EUnetHTA Joint Action 2 Work Package 8. HTA Core Model ® version 3.0 (PDF) 2016. Available from: www.htacoremodel.info/BrowseModel.aspx, Accessed 1-11-2018.

81. Leali PT, Solla F, Maestretti G, et al. Safety and efficacy of vertebroplasty in the treatment of osteoporotic vertebral compression fractures: A prospective multicenter international randomized controlled study. *Clinical Cases in Mineral and Bone Metabolism* 2016;13(3):234-36.

82. Hsiehchen D, Espinoza M, Hsieh A. The Cooperative Landscape of Multinational Clinical Trials. *PloS one* 2015;10(6):e0130930-e30.

83. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* (in press)

84. Borgstrom F, Beall DP, Berven S, et al. Health economic aspects of vertebral augmentation procedures. *Osteoporos Int* 2015;26(4):1239-49.

85. Fritzell P, Ohlin A, Borgström F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: a Swedish multicenter randomized controlled trial with 2-year follow-up. *Spine* 2011;36(26):2243-51.

86. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet* 2010a;376(9746):1085-92.

87. Stevenson M, Gomersall T, Lloyd Jones M, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2014;18(17):1-290.

88. Strom O, Leonard C, Marsh D, et al. Cost-effectiveness of balloon kyphoplasty in patients with symptomatic vertebral compression fractures in a UK setting. *Osteoporos Int* 2010;21(9):1599-608.

89. Svedbom A, Alvares L, Cooper C, et al. Balloon kyphoplasty compared to vertebroplasty and nonsurgical management in patients hospitalised with acute osteoporotic vertebral compression fracture: a UK cost-effectiveness analysis. *Osteoporos Int* 2013;24(1):355-67.

90. Takahashi S, Hoshino M, Yasuda H, et al. Cost-effectiveness of Balloon Kyphoplasty for Patients With Acute/Subacute Osteoporotic Vertebral Fractures in the Super-Aging Japanese Society. *Spine* 2019;44(5):E298-E305.

91. Marschner M, Stroszczynski C. [Patient information and informed consent in interventional radiology]. *Radiologe* 2008;48(2):171-4.

92. Mezrich JL, Resnik CS. Panacea or Sham? Legal Issues of Vertebroplasty. *J Am Coll Radiol* 2016;13(6):663-5.

93. Settlement on kyphoplasty billing. *OR Manager* 2009;25(7):6-7.

94. Klezl Z, Bhangoo N, Phillips J, et al. Social implications of balloon kyphoplasty: prospective study from a single UK centre. *Eur Spine J* 2012;21(9):1880-6.

95. Carr D, Cook R, Tong D, et al. Kyphoplasty patient-centered outcomes via questionnaire. *J Spine Surg* 2018;4(2):328-32.

96. Wasfie T, Jackson A, Brock C, et al. Does a fracture liaison service program minimize recurrent fragility fractures in the elderly with osteoporotic vertebral compression fractures? *American Journal of Surgery* 2019;217(3):557-60.

97. Johnson J, Rogers W, Jeffree RL. The controversy over vertebroplasty: an analysis of the debate and proposals for a way forward. *J Med Imaging Radiat Oncol* 2012;56(4):449-51.

98. Miller FG, Kallmes DF, Buchbinder R. Vertebroplasty and the placebo response. *Radiology* 2011;259(3):621-5.

99. Munk PL, Liu DM, Murphy KP, et al. Effectiveness of vertebroplasty: a recent controversy. *Can Assoc Radiol J* 2009;60(4):170-1.

100. Orr RD. Vertebroplasty, cognitive dissonance, and evidence-based medicine: what do we do when the 'evidence' says we are wrong? *Cleve Clin J Med* 2010;77(1):8-11.

101. Wagner AL. Vertebroplasty and the randomized study: where science and ethics collide. *AJNR Am J Neuroradiol* 2005;26(7):1610-1.

102. Martinez-Ferrer A, Blasco J, Carrasco JL, et al. Risk factors for the development of vertebral fractures after percutaneous vertebroplasty. *J Bone Miner Res* 2013;28(8):1821-9.

103. Efficacy and safety of vertebroplasty for treatment of painfulosteoporotic vertebral fractures: a randomised controlled trial[ACTRN012605000079640]. *BMC Musculoskeletal Disorders* 2008;9:156-64.

104. Kroon F, Staples M, Ebeling PR, et al. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. *J Bone Miner Res* 2014;29(6):1346-55.

105. Buchbinder R, Osborne RH, Ebeling PR, et al. Efficacy and safety of vertebroplasty for treatment of painful osteoporotic vertebral fractures: a randomised controlled trial [ACTRN012605000079640]. *BMC Musculoskelet Disord* 2008;9:156-56.

106. Staples MP, Howe BM, Ringler MD, et al. New vertebral fractures after vertebroplasty: 2-year results from a randomised controlled trial. *Arch Osteoporos* 2015;10:229.

107. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine* 2011;14(5):561-9.

108. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009;361(6):569-79.

109. Gray LA, Jarvik JG, Heagerty PJ, et al. INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST): a randomized controlled trial of percutaneous vertebroplasty. *BMC musculoskeletal disorders* 2007;8:126-26.

110. Comstock BA, Sitlani CM, Jarvik JG, et al. Investigational vertebroplasty safety and efficacy trial (INVEST): patient-reported outcomes through 1 year. *Radiology* 2013;269(1):224-31.

111. Klazen CA, Venmans A, de Vries J, et al. Percutaneous vertebroplasty is not a risk factor for new osteoporotic compression fractures: results from VERTOS II. *AJNR Am J Neuroradiol* 2010b;31(8):1447-50.

112. Venmans A, Klazen CA, Lohle PN, et al. Percutaneous vertebroplasty and pulmonary cement embolism: results from VERTOS II. *AJNR Am J Neuroradiol* 2010;31(8):1451-3.

113. Venmans A, Klazen CA, van Rooij WJ, et al. Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary--results from VERTOS II. *Neuroradiology* 2011;53(1):19-22.

114. Rousing R, Hansen KL, Andersen MO, et al. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. *Spine (Phila Pa 1976)* 2010;35(5):478-82.

115. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful

osteoporotic vertebral compression fractures. The VERTOS study. *AJNR Am J Neuroradiol* 2007;28(3):555-60.

116. Eidt-Koch D, Greiner W. Quality of life results of balloon kyphoplasty versus non surgical management for osteoporotic vertebral fractures in Germany. *Health Economics Review* 2011;1(1):1-7.

117. Van Meirhaeghe J, Bastian L, Boonen S, et al. A randomized trial of balloon kyphoplasty and nonsurgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. *Spine* 2013;38(12):971-83.

118. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009;373(9668):1016-24.

12. Appendices

12.1 Appendix A: Sources of Literature (databases)

Table 16 Databases searched and number of search results

Source	Location	Search results
PubMed	https://www.ncbi.nlm.nih.gov	2,773
Embase	https://www.embase.com/	4,696
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/	453
Cinahl	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete	472
York CRD (inc. HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/CRDWeb/	106
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	5
Econlit	https://www.aeaweb.org/econlit/	8
ETHMED	http://www.ethicsweb.eu/search_ets	10
	Total	**8,523**

Search strategy – Medline [Inception to 4 April 2019]

No.	Query	Results
1.	Spinal fractures[Text Word]	NR
2.	Spinal fractures[MeSH Terms]	NR
3.	Osteoporotic fractures[Text Word]	NR
4.	Osteoporotic fractures[MeSH Terms]	NR
5.	Compression fracture[Text Word]	NR
6.	Compression fracture[MeSH Terms]	NR
7.	Spinal fracture[Text Word]	NR
8.	Spinal fracture[MeSH Terms]	NR
9.	Spinal tumor[Text Word]	NR
10.	Spinal tumor[MeSH Terms]	NR
11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	NR
12.	Vertebroplasty[Text Word]	NR

13.	Vertebroplasty[MeSH Terms]	NR
14.	Kyphoplasty[Text Word]	NR
15.	Kyphoplasty[MeSH Terms]	NR
16.	Sarcoplasty[Text Word]	NR
17.	Cementoplasty[Text Word]	NR
18.	Cementoplasty[MeSH Terms]	NR
19.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	2773

Abbreviations: NR = not reported

Search strategy – Embase [Inception to 4 April 2019]

No.	Query	Results
1.	Kyphoplasty/exp or Kyphoplasty.mp.	3370
2.	Sarcoplasty.mp	3
3.	Vertebroplasty.mp.	5760
4.	Pediculoplasty.mp.	11
5.	Cementoplasty.mp. or Cementoplasty/exp	6832
6.	Percutaneous vertebroplasty.mp. or Percutaneous vertebroplasty/exp	6678
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	7529
8.	Spinal fractures.mp. or Spine fracture/exp	23439
9.	Osteoporotic fractures.mp. or Fragility fracture/exp	18967
10.	Fractures, compression.mp. or Compression fracture/exp	5366
11.	Compression fracture.mp.	5991
12.	Spinal fracture.mp. or Spine fracture/exp	22970
13.	Spinal tumor/exp	7958
14.	#8 OR #9 OR #10 OR #11 OR #12 OR #13	46531
15.	#7 AND #14	4696

Search Strategy – Cochrane [Inception to 4 April 2019]

No.	Query	Results
1.	MeSH descriptor: [Vertebroplasty] explode all terms	121
2.	(vertebroplasty);ti,ab,kw	334
3.	#1 OR #2	363
4.	MeSH descriptor: [Kyphoplasty] explode all trees	49
5.	(kyphoplasty):ti,ab,kw	218
6.	#4 OR #5	218
7.	#3 AND #6	453

Search strategy – CINAHL [Inception to 5 April 2019]

No.	Query	Results
1.	TX Vertebroplasty	1441
2.	TX Kyphoplasty	1386
3.	TX Cementoplasty	0
4.	TX Sarcoplasty	0
5.	TX Percutaneous vertebroplasty	687
6.	#1 OR #2 OR #3 OR #4 OR #5	2073
7.	TX Spinal fracture	12057
8.	TX Osteoporotic fractures	5877
9.	TX Compression fractures and osteoporosis	1786
10.	TX Compression fracture of the spine	2834
11.	TX Compression fracture pain	4183
12.	#7 OR #8 OR #9 OR #10 OR #11	16240
13.	#6 and #12	472

Search Strategy – York CRD (including DARE, NHS EED, HTA) [Inception to 8 April 2019]

No.	Query	Results
1.	Vertebroplasty[Any field]	91
2.	Kyphoplasty[Any field]	73
3.	#1 OR #2	106

Search strategy – CEA Registry [Inception to 8 April 2019]

No.	Query	Results
1.	TX Vertebroplasty	4
2.	X Kyphoplasty	4
3.	#1 OR #2	5

(All but one was also captured in PubMed search)

Search strategy – Econlit [Inception to 8 April 2019]

No.	Query	Results
1.	TX Vertebroplasty	8
2.	X Kyphoplasty	2
3.	#1 OR #2	8

Search strategy – Ethicsweb [Inception to 8 April 2019]

No.	Query	Results
1.	TX Vertebroplasty	10
2.	X Kyphoplasty	2
3.	#1 OR #2	10

Table 17 Sources of literature (websites) to be searched in the HTA phase

HTA Websites	
International	
National Information Centre of Health Services Research and Health Care Technology (NICHSR)	https://www.nlm.nih.gov/nichsr/db.html
National Library of Medicine Health Services/Technology Assessment Texts (HSTAT)	https://www.ncbi.nlm.nih.gov/books/NPBK16710/
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/
Centre for Clinical Effectiveness, Monash University	http://monashhealth.org/health-professionals/cce/
Centre for Health Economics, Monash University	https://www.monash.edu/business/che
National Health and Medical Research Council	https://www.nhmrc.gov.au/

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)	http://www.coagcouncil.gov.au/
Austria	
Institute of Technology Assessment / HTA unit	https://www.oeaw.ac.at/ita/publikationen/
Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)	https://hta.lbg.ac.at/page/publikationen/en
Gesunheit Österreich GmbH (GOG)	http://www.goeg.at
Hauptverband der Österreichischen Sozialversicherungsträger (HVB)	http://www.sozialversicherung.at
University for Health Sciences, Medical Informatics and Technology	https://www.umit.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Scientific Institute of Public Health (IPH)	https://www.wiv-isp.be/en
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV-INAMI)	https://www.inami.fgov.be/
Bulgaria	
National Center of Public Health Analyses (NCPHA)	https://www.ncpha.government.bg
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://www.conitec.gov.br/
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
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/
The Canadian Association for Health Services and Policy Research (CAHSPR)	https://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org/
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca/
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca/
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca/
Evidence Development and Standards Branch (HQO)	http://www.hqontario.ca

Croatia	
Ministry of Health of the Republic of Croatia (MIZ)	https://www.miz.hr
Croatian Health Insurance Fund (CHIF)	https://www.hzzo.hr
Croatian Institute of Public Health (CIPH)	https://www.hzjz.hr/english/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Cyprus	
Ministry of Health Cyprus (MoH Cyprus)	https://www.eunethta.eu/moh-cyprus
Czech Republic	
Ministry of Health Czech Republic (MoH Czech)	https://www.mzcr.cz/en
State Institute for Drug Control (SUKL)	https://www.sukl.eu
Denmark	
Danish National Institute of Public Health	https://www.sdu.dk/en/sif/forskning
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Estonia	
Institute of Family Medicine and Public Health (UTA)	https://www.tervis.ut.ee
Finland	
Finnish National Institute for Health and Welfare	https://thl.fi/en/web/thlfi-en/publications
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	http://www.fincchta.fi
Finnish Medicines Agency (FIMEA)	http://www.fimea.fi
National Institute for Health and Welfare (THL)	https://www.thl.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)	info.cedit@sap.aphp.fr
Germany	
German Institute for Medical Documentation and Information (DIMDI)	https://www.dimdi.de/
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	http://www.g-ba.de
Greece	
Institute of Pharmaceutical Research and Technology (IFET)	http://www.ifet.gr/english_site/
National and Kapodistrian University of Athens (EKAPTY-NKUA)	http://www.phs.uoa.gr/
National Evaluation Centre of Quality and Technology in S.A-EKAPTY	http://www.ekapty.gr/
National Organization for Medicines (EOF)	http://www.eof.gr

National Organisation for Healthcare Provision (EOPYY)	http://www.eopyy.gov.gr
Onassis Cardiac Surgery Centre (OCSC)	http://www.onasseio.gr/
Hungary	
Health Services Management Training Center (SU)	http://www.semmelweis.hu/emk/en/
National Institute of Pharmacy and Nutrition (NIPN)	http://www.ogyei.gov.hu/main_page/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
National Centre for Pharmacoeconomics, St James Hospital (NCPE)	http://www.ncpe.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
Centro Regionale Unico sul Farmaca del Veneta (CRUF/AOUIVR)	http://www.ospedaleuniverona.it/ecm/home
HTA Unit in A. Gemelli Teaching Hospital (UVT)	http://www.policlinicogemelli.it/area/?s=206
Italian Medicines Agency (AIFA)	http://www.agenziafarmaco.gov.it
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Regione Del Veneto – Area Sanita E' Sociale (Veneto/CRUF)	http://www.ospedaleuniverona.it/ecm/home
Regione Emilia-Romagna (RER)	http://www.regione.emilia-romagna.it/
Sede del Ministro – Ministero della salute (DGFDM IT)	http://www.salute.gov.it
University Hospital A. Gemelli (UCSC GEMELLI)	http://www.roma.unicatt.it/
Unita di Valutazione Technology Assessment (UVTA/AOP)	http://www.sanita.padova.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Latvia	
National Health Service (NVD)	http://www.vmnd.gov.lv/
Lithuania	
The Institute of Hygiene (HI)	http://www.hi.lt
State Health Care Accreditation Agency (VASPVT)	http://www.vaspvt.gov.lt
Luxembourg	
Inspection Générale de la Sécurité Sociale (IGSS), Cellule d'Expertise Médicale (CEM)	http://www.mss.public.lu/publications/index.html
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
Malta	

Directorate for Pharmaceutical Affairs (DPA/MoH Malta)	http://www.health.gov.mt/en/pharmaceutical/Pages/pharmaceutical-affairs.aspx
Mexico	
Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)	www.cenetec.gob.mx
Norway	
Norwegian Knowledge Centre for the Health Services	https://www.fhi.no/sys/ks/
Norwegian Institute of Public Health (NIPH)	http://www.fhi.no
The Netherlands	
Erasmus Universiteit Rotterdam (EUR)	http://www.eur.nl/
Health Council of the Netherlands (Gezondheidsraad)	https://www.gezondheidsraad.nl/
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Utrecht University (UU)	http://www.uu.nl
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Norwegian Directorate of Health (Hdir)	http://helsedirektoratet.no/english
Norwegian Medicines Agency (NOMA)	http://www.legemiddelverket.no
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Portugal	
Administração Central do Sistema de Saúde, I.P. (ACSS IP)	http://www.acss.min-saude.pt
National Authority of Medicines and Health Products (INFARMED)	http://www.infarmed.pt
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Romania	
Babes-bolayi University, Cluj School of Public Health (UBB)	http://publichealth.ro/
Institutu National De Sanatate Publica (INSP/NIPHB)	http://www.inspo.gov.ro
National School of Public Health, Management and Professional Development (NSPHMPDB)	http://www.snspms.ro
Singapore	
Agency for Care Effectiveness (ACE)	http://www.ace-hta.gov.sg/
Slovakia	
Comenius University in Bratslava (UniBA FOF)	https://uniba.sk/en/
Ministry of Health of the Slovak Republic (MoH Slovak Republic)	http://www.health.gov.sk
Slovenia	

Ministry of Health of the Republic of Slovenia (MoH Slovenia)	http://www.mz.gov.si/en/
National institute of Public Health (NIJZ)	http://www.nijz.si
Public Agency of the Republic of Slovenia for Medical Products and Medical Devices (JAZMP)	http://www.jazmp.si/en/
South Africa	
Charlotte Maxeke Research Consortium (CMeRC)	http://www.cmerc.org
Spain	
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	http://www.aemps.gob.es
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	http://www.aetsa.org/
Basque Foundation for Health Innovation and Research (BIOEF)	http://www.bioef.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
Directorate General for Pharmacy and Health Care Products (DGFPS MSPSI)	website not provided
Evaluation AND Planning Unit – Directorate of the Canary Islands Health Service (SESCS)	http://www.sescs.es
Fundación Canaria de Investigación Sanitaria (Funcanis)	http://www.funcanis.org/
Fundacion Profesor Novoa Santos (AVALIA FNS)	http://www.fundacionprofesornovoasantos.org/es/
Fundación Pública Andaluza Progreso y Salud (FPS)	http://www.juntadeandalucia.es/fundacionprogresoysalud/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
The Instituto De Salud Carlos III (AETS-ISCIIIS)	http://www.eng.isciii.es
Sweden	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Dental and Pharmaceutical Benefits Agency (TLV)	http://www.tlv.se
Medical Products Agency (MPA)	http://www.lakemedelsverket.se
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
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/

Swiss Society of Neurosurgery	https://www.swissneurosurgery.ch/Home
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr)
United Kingdom	
All Wales Therapeutics and Toxicity Centre (AWTTC)	http://awttc.org
Health Information Quality Authority (HIQA)	http://www.hiqa.ie
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
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
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/
Office of Health Technology Assessment Archive (US)	http://ota.fas.org/
U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (Tec)	https://www.bcbs.com/news/press-releases/blue-cross-blue-shield-association-launches-evidence-street-website-streamline
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm
Ukraine	
Department of HTA at the State Expert Centre of the Ministry of Health (SEC)	website not provided
Uruguay	
Health Assessment Division, Ministry of Public Health, (HAD)	http://www.msp.gub.uy
Clinical trial registries	
ClinicalTrials.gov	https://clinicaltrials.gov/
Cochrane Central Register of Controlled Trials	https://www.cochranelibrary.com/central
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/ctr-search/search

WHO International Clinical Trials Registry Platform (ICTRP)	http://www.who.int/ictrp/en/
Current Controlled Trials MetaRegister	http://www.isrctn.com
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/
Grey literature sources	
New York Academy of Medicine Grey Literature Report	http://www.greylit.org
University of York Centre for Research and Dissemination (York CRD)	https://www.crd.york.ac.uk/CRDWeb/
TRIP Database	http://www.tripdatabase.com/
Specialty websites	
Geneva Medical Association	https://www.amge.ch/
Eular	https://www.eular.org/index.cfm
European Geriatric Medicine Society	https://www.eugms.org/home.html
Australia and New Zealand Society for Geriatric Medicine	http://www.anzsgm.org/
Swiss Orthopaedic Association	http://www.swissorthopaedics.ch/de/
American Orthopaedic Association	http://www.aoassn.org/aoaimis/aoanew
Australian Orthopaedic Association	https://www.aoa.org.au/
Australian Society of Orthopaedic Surgeons	http://www.asos.org.au/
British Orthopaedic Association	https://www.boa.ac.uk/
Canadian Orthopaedic Association	http://coa-aco.org/
Swiss Society for Neuroscience	https://www.swissneuroscience.ch/
Neurosurgical Society of Australasia	http://www.nsa.org.au/
Swiss Society of Spinal Surgery	https://www.spinesociety.ch/
North American Spine Society	https://www.spine.org/
International Osteoporosis Foundation	https://www.iofbonehealth.org/
Osteoporosis Australia	https://www.osteoporosis.org.au/
Society of Interventional Radiology	https://www.sirweb.org/
Clinical practice guidelines	
Guidelines International Network (GIN)	https://www.g-i-n.net/library/international-guidelines-library
Association of Scientific Medical Societies (AWMF)	https://www.awmf.org/awmf-online-das-portal-der-wissenschaftlichen-medizin/awmf-aktuell.html
National Guideline Clearinghouse	https://www.ahrq.gov/gam/index.html
Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/guidelines/published/

12.2 Appendix B: Characteristics of Included Studies

Table 18 Characteristics of included RCTs for safety, efficacy and effectiveness of PVP

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Blasco et al. 2012[8] [102] Spain	OVCF from T4–L5 clinical onset <12 months, pain measured as VAS ≥4, confirmed by X-ray and presence of oedema on MRI or activity on bone scan n=125	RCT, open-label 12 months Single centre (Recruited from: primary care centres, specialists from hospital inpatient, outpatient & emergency departments)	**PVP** (Bilateral, transpedicular, PMMA cement, in C-arm or in a biplane angiography suite) **Non-surgical treatment** (Analgesics & rescue therapy)	**Effectiveness** • Pain (VAS) • Quality of life (QUALEFFO) • Medication use (analgesics, NSAIDs & opiate derivatives) • Treatment failure (need for rescue therapy) **Safety** • Complications i.e. cement leakage • Incident vertebral fractures
Buchbinder et al. 2009[7] [103] Kroon et al. 2014[104] Staples et al. 2015[105] [106] Australia	Back pain <12 months, 1-2 recent vertebral facture (collapse grade 1 or higher), MRI confirmed acute VCF (oedema or fracture line). n=78	RCT, double-blinded 24 months Multicentre (n=4, recruited from: general practitioners, specialists at hospital inpatient and emergency departments)	**PVP** (PMMA cement, unipedicular, biplane imaging or image intensifier screen rotated to monitor progress) **Sham** (Sham procedure, subcutaneous lidocaine injection with needle advancement and tapping, mimicking PVP procedures)	**Efficacy** • Pain (VAS, NRS) • Function (RDQ) • Quality of life (TTO, QUALEFFO, EQ-5D, AqoL) • Back pain-related disability (modified Roland Scale) • Patient's perceived recovery (7-point scale) • Analgesic use **Safety** • Incident vertebral fracture • Other adverse events
Clark et al. 2016[2] Australia **VAPOUR**	Osteoporotic patients, 1 or 2 VCF < 6 weeks, pain NRS > 7, MRI confirmed VCF. n=120	RCT, double-blinded 6 months Multicentre (n=4, interventional radiology clinics)	**PVP** (PMMA cement, unipedicular or bipedicular, fluoroscopic guidance) **Sham** (Sham procedure, blunt needle advancement and tapping, mimicking PVP procedures)	**Efficacy** • Pain (VAS, NRS) • Quality of life (QUALEFFO, SF-36, EQ-5D) • Physical function (RDQ) • Analgesic use **Safety** • Cement leakage • Incidental vertebral fracture • Other adverse events • Mortality

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Farrokhi, Alibai & Maghami 2011[107] Iran	Patients with OVCF with 10-70% vertebral height loss, severe back pain refractory to analgesics for ≥4 weeks to 1 year, focal tenderness of clinical exam related to fracture level, bone attenuation, bone oedema or vacuum phenomenon on MRI, unresponsive to medical therapy n=82	RCT, single-blinded 36 months Single centre (recruited from: outpatient centres)	**PVP** (Unilateral, PMMA cement, fluoroscopic guidance) **Non-surgical treatment** (optimal medical management i.e. mix of paracetamol, codeine, ibuprofen, calcium, vitamin D, alendronate and calcitonin)	**Effectiveness** • Pain (VAS) • Pain and lower back pain-related disability (questionnaire) • Functional Quality of Life (ODI) • Vertebral height & sagittal index (x-ray) **Safety** • Adjacent level fractures • Cement leakage
Firanescu et al. 2011[25] Firanescu et al. 2018[22] Firanescu et al. 2019[3] Netherlands **VERTOS IV**	1-3 painful (VAS ≥5) thoracolumbar OVCF of up to 6 weeks duration[2], diminished bone density (T score -1 or less), ≥15% loss of vertebral height, bone oedema on MRI n=180	RCT, double-blinded 12 months Multicentre (n=4, recruited from: outpatient clinics)	**PVP** (Transpedicular, bilateral, PMMA cement, post-op CT for cement extravasation) **Sham** (Sham vertebroplasty procedure without cement injection)	**Efficacy** • Pain (VAS) • Quality of life (QUALEFFO) • Physical function (RDQ) • Patient satisfaction • Vertebral height loss • Analgesic usage **Safety** • Adverse events • Subsequent vertebral fracture

[2] After 6 months the authors broadened the inclusion to patients with fractures up to 9 weeks old, due to recruitment difficulties.

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Kallmes et al. 2009 [108] Comstock et al. 2013[109] [110] USA UK Australia **INVEST**	1-3 OVCFs from T4–L5, VCF <12 months, in patients >50 years, refractory to medical therapy, with pain score at least 3/10 n=131	RCT, double-blinded 12 months Multicentre (n=11, recruited from: outpatient clinics)	**PVP** (PMMA cement, in fluoroscopy suite, under conscious sedation, unilateral) **Sham** (Sham procedure, needle insertion, no cement injection)	**Efficacy** • Pain (Charlson comorbidity index, Pain Frequency Index, Pain Bothersomeness Index) • Function (SOF-ADL, OPAQ, RDQ) • Quality of life (SOF, ADL, EQ-5D, modified Deyo-Patrick Pain Frequency and Bothersomeness Scale, SF-36) • Opioid medication use **Safety** • Adverse events
Klazen et al. 2010a[86] Klazen et al. 2010b[111] Venmans et al. 2010[112] Venmans et al. 2011[113] Netherlands **VERTOS II**	Painful (VAS≥5) thoracolumbar OVCF, minimum 15% height loss, back pain for 6 weeks or less, bone oedema on MRI, focal tenderness on physical examination, decreased bone density (T scores ≤–1). N=202	RCT, open-label 12 months Multicentre (n=5, recruited from: radiology departments)	**PVP** (Transpedicular, bilateral, PMMA cement, continuous fluoroscopic monitoring for cement extravasation) **Non-surgical treatment** (Pain medication. Analgesics in ascending order: paracetamol, tramadol, tramadol and paracetamol, morphine. Osteoporosis medication)	**Effectiveness** • Pain (VAS) • Quality of life (QUALEFFO, EQ-5D) • Physical function (RDQ) • Vertebral height loss • Analgesic usage **Safety** • Adverse events • Cement leakage (CT imaging) • Subsequent vertebral fracture (x-ray imaging) • Mortality

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Leali et al. 2016[81] Italy France Switzerland	Post-menopausal women, one thoracolumbar OVCF (primary or secondary osteoporosis), acute pain from severe fracture (not defined), bone oedema present on MRI. n=400	RCT 6 months Multicentre (n=4)	**PVP** (Transpedicular, PMMA cement, fluoroscopic monitoring, osteoporosis medication and pain medication) **Non-surgical treatment** (Pain medication, osteoporosis medication, physiotherapy or bracing)	**Effectiveness** • Pain (VAS) • Physical function (ODI) **Safety** • Adverse events • Mortality
Rousing et al. 2009[23] Rousing et al. 2010[114] Denmark	OVCF with intractable pain less than 8 weeks, MRI confirmed VCF. n=49	RCT, open-label 12 months Single centre	**Vertebroplasty** (PMMA cement, fluoroscopic monitoring for cement extravasation) **Non-surgical treatment** (Brace treatment, pain medication, general mobilising physiotherapy)	**Effectiveness** • Pain (VAS) • Physical function (DPQ, timed up and go tests, repeated chair test, tandem test) • Quality of life (SF-36, EQ-5D, Barthel index) • Cognitive function (MMSE) **Safety** • New fracture • Mortality • Adverse events

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Voormolen et al. 2007[115] Netherlands VERTOS I	OVCF with min. 15% height loss on spine X-ray, invalidating back pain relating to the fracture with 6 weeks to 6 months duration refractory to medical therapy, focal tenderness related to level of fracture on exam, bone attenuation T-scores less than -2.0, bone marrow oedema of fracture on spine MRI, patient aged ≥50 years n=34	RCT, open-label 12 months Multicentre (n=3, recruiting centre NR)	**PVP** (Transpedicular, PMMA cement, under constant fluoroscopy) **Non-surgical treatment** (Optimal pain medication i.e. paracetamol, NSAIDs, or opiate derivatives)	**Effectiveness** • Pain (VAS) • Analgesic use • Physical function (RDQ) • QoL (QUALEFFO) **Safety** • Complications
Wang et al. 2016[5] China	Severe pain caused by acute (fracture occurred within 2 weeks) or subacute (fracture occurred within 2–8 weeks) OVCFs n=206	RCT, open-label 12 months Single centre	**Vertebroplasty** (PMMA cement, fluoroscopic guidance, transpedicular, unilateral or bilateral) **Facet blocking** (Bilateral posterior needle inserting lidocaine and prednisolone into facet joint capsule, under fluoroscopic monitoring)	**Efficacy** • Pain (VAS) • Physical function (ODI, RDQ) • Quality of life (SF-36) **Safety** • New fracture • Complications

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Yang et al. 2016[6] China USA	Patients with OVCF from acute mild/minor trauma, with back pain (VAS ≥5), low signal on T1-weighted and high signal on T2-weighted MRI, fracture level T5 or lower, living independently without need for wheelchair prior to trauma, decreased BMD (T score ≥-1) n=107	RCT 12 months Multicentre (n=4, recruited from: emergency room or outpatient clinics)	**PVP** (Transpedicular, PMMA cement, under fluoroscopic guidance) **Non-surgical treatment** (Bed rest, bracing, physiotherapy & NSAIDs. Tramadol and morphine if needed)	**Effectiveness** • Pain (VAS) • HR-QoL (ODI, QUALEFFO) • Patient satisfaction (survey) **Safety** • Cement leakage • Incident vertebral fracture (x-ray then MRI to confirm)

Abbreviations: ADL = Activities of Daily Living, **AQoL** = Assessment of Quality of Life, **BMD** = bone mineral density, **CT** = computed tomography, **DPQ** = Dallas Pain Questionnaire, **EQ-5D** = EuroQol 5-dimension scale, **HR-QoL** = Health-related quality of life, **MMSE** = mini-mental state examination, **MRI** = magnetic resonance imaging, **NR** = not reported, **NRS** = numerical rating scale, **NSAIDs** = nonsteroidal anti-inflammatory drugs, **ODI** = Oswestry Disability Index, **OPAQ** = Osteoporosis Assessment Questionnaire, **OVCF** = osteoporotic vertebral compression fracture, **PMMA** = Polymethyl methacrylate, **PVP** = percutaneous vertebroplasty, **QUALEFFO** = Quality of Life Questionnaire of the European Foundation for Osteoporosis, **RCT** = randomised controlled trial, **RDQ** = Roland-Morris Disability Questionnaire, **SF-36** = 36-item Short Form general health survey, **SOF-ADL** = Study of Osteoporotic Fractures—Activities of Daily Living, **SOF** = Strength of Function, **TTO** = time-trade off, **VAS** = visual analogue scale, VCF = vertebral compression fracture

Table 19 Characteristics of included RCTs for safety, efficacy and effectiveness of PBK

Author, year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Eidt-Koch & Greiner 2011[116] Eidt-Koch & Greiner 2011[116] Germany	Patients >50 years with ≥1 acute (≤3 months) painful (VAS≥5) thoracolumbar OVCF N=82	RCT 12 months Multicentre (n=8)	**Balloon kyphoplasty** (PMMA cement, balloon deflated and removed) **Non-surgical treatment** (Analgesics, bed rest, back bracing & physiotherapy)	**Effectiveness** • Quality of life (EQ-5D, RDQ)
Jin et al. 2018[26] China	Single level thoracolumbar OVCFs in patients ≥60 years, local pain and injured vertebra on clinical exam, linear black signal on MRI n = 41	RCT, open-label 12 months Single centre	**Balloon kyphoplasty** (PMMA cement, transpedicular, unilateral, fluoroscopic guidance, balloon deflated and removed) **Non-surgical treatment** (Analgesics & anti-osteoporosis treatment)	**Effectiveness** • Pain (VAS) • Physical/mental functioning (SF-36) • Kyphosis angle & anterior vertebral body height (radiographic data)
Li, Zhu & Xie 2017[41] China	Elderly OVCF patients: age ≥65 years, duration 2 hours to 2 weeks, fracture confirmed with x-ray, CT or MRI scans n = 80	RCT, open-label 6 months Single centre	**Balloon kyphoplasty** (PMMA cement under constant fluoroscopic guidance, balloon deflated and removed) **Non-surgical treatment** (Physiotherapy & bed rest)	**Effectiveness** • Pain (VAS) • Height of vertebrae (x-ray imaging) • Kyphosis (Cobb angle) • Low back pain (ODI) **Safety** • Complications i.e. spinal cord injury

Author, year; country; trial name	Inclusion criteria; Sample size	Design; Follow-up; Setting	Intervention; Comparator	Relevant outcomes
Liu, Cao & Kong 2019[40] China	Multiple OVCFs confirmed with x-ray and CT scans n = 116	RCT, open-label Post-operatively Single centre (Recruited from: inpatient)	**Balloon kyphoplasty** (Cement type not reported, fluoroscopic guidance, balloons injected with cement) **Non-surgical treatment** (Analgesics, physiotherapy, fixation & bed rest)	**Effectiveness** • Pain (VAS) • Height of trailing edge, leading edge, midcourt line & upper thoracic kyphosis (imaging) • Daily life disturbance (Barthel Index) **Safety** • Complications i.e. cement leakage, venous embolism, decubitus, infection • Adverse events i.e. sudden hypotension, arrhythmia, cardiac arrest
Van Meirhaeghe et al. 2013[117] Wardlaw et al. 2009[118] Austria Belgium France Germany Italy Sweden Netherlands UK **FREE trial**	>1 acute T5–L5 VCF, bone marrow signal changes on MRI, decreased height compared with adjacent vertebrae, pain score at least 4/10, >1 with 15% n=147	RCT, open-label 24 months Multicentre (n=21)	**Balloon kyphoplasty** (PMMA cement, fluoroscopic guidance) **Non-surgical treatment** (Analgesics, bed rest, bracing, physiotherapy, rehabilitation programs, and walking aids, calcium and vitamin D)	**Effectiveness** • Quality of Life (SF-36, EQ-5D) • Physical function (RDQ) • Pain (VAS) • **Safety** • Adverse events • Incident vertebral fracture

Abbreviations: EQ-5D = EuroQol 5-dimension scale, **CT** = computed tomography, **MRI** = magnetic resonance imaging, **ODI** = Oswestry Disability Index, **OVCF** = osteoporotic vertebral compression fracture, **PMMA** = Polymethyl methacrylate, **RCT** = randomized controlled trial, **RDQ** = Roland-Morris Disability Questionnaire, **SF-36** = 36-item Short Form general health survey, **VAS** = visual analogue scale, **VCF** = vertebral compression fracture.