

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures

Technology appraisal guidance

Published: 24 April 2013

www.nice.org.uk/guidance/ta279

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1 Recommendations

- 1.1 Percutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people:
- who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management **and**
 - in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging.

2 Clinical need and practice

- 2.1 Vertebral fracture refers to a break in any of the bones (vertebrae) of the spinal column. Vertebral compression fractures usually occur when the front of the vertebral body collapses, and may be caused by trauma, cancer or osteoporosis. Osteoporotic vertebral compression fractures can cause the spine to curve and lose height, and can result in pain, difficulties in breathing, gastrointestinal problems, sleep disturbances and difficulties in performing activities of daily living. High doses of analgesics used to treat such pain can have significant adverse effects. The symptoms and treatment of osteoporotic vertebral compression fractures can worsen quality of life and cause loss of self-esteem.
- 2.2 The prevalence of vertebral fractures increases with age and is more common in women. It is estimated that approximately 2.5 million people in England and Wales have osteoporosis. The prevalence of osteoporotic vertebral compression fractures is difficult to estimate because not all fractures come to the attention of clinicians and they are not always recognised on X-rays. Clinically evident osteoporotic vertebral compression fractures are associated with an increase in mortality.
- 2.3 Treating vertebral compression fractures aims to restore mobility, reduce pain and minimise the incidence of new fractures. Non-invasive treatment (such as pain medication, bed rest, and back braces) focuses on alleviating symptoms and supporting the spine. [NICE's interventional procedures guidance on percutaneous vertebroplasty](#) and [NICE's interventional procedures guidance on balloon kyphoplasty for vertebral compression fractures](#) support the use of percutaneous vertebroplasty and percutaneous balloon kyphoplasty without stenting (hereafter vertebroplasty and kyphoplasty respectively) as options for treating vertebral fractures. These guidance documents note that patients should receive these procedures only after discussion with a specialist multidisciplinary team, and in an appropriately resourced facility that has access to a spinal surgery service. For vertebroplasty, the guidance also states that the procedure should be limited to people whose pain does not respond to more conservative treatment.

3 The technologies

Percutaneous vertebroplasty

- 3.1 Vertebroplasty involves injecting bone cement, typically polymethylmethacrylate, into the vertebral body (the solid part of the vertebra), using local anaesthetic and an analgesic. Vertebroplasty aims to relieve pain in people with painful fractures and to strengthen the bone to prevent future fractures.
- 3.2 Several bone cements are available for vertebroplasty. The acquisition cost of the high-viscosity Confidence Spinal Cement System (Johnson and Johnson) is based on the number of vertebrae being treated. The average cost of the kit is £1,472. Low-viscosity cements are available and, based on list prices provided by 2 manufacturers (Cook and Stryker); the Assessment Group estimated a cost of £800 per low-viscosity cement vertebroplasty procedure.

Percutaneous balloon kyphoplasty without stenting

- 3.3 Kyphoplasty involves inserting a balloon-like device (tamps) into the vertebral body, using local or general anaesthetic. The balloon is slowly inflated until it restores the normal height of the vertebral body or the balloon reaches its highest volume. When the balloon is deflated, the space is filled with bone cement, and a stent may or may not be placed. This document covers kyphoplasty without stenting. Kyphoplasty aims to reduce pain and curvature of the spine.
- 3.4 The Kyphon BKP kit (Medtronic) is available in the UK for kyphoplasty. Kyphon BKP is a CE-marked, single-use sterile pack with a list price of £2,600.50 and includes 2 Kyphon Xpander inflatable bone tamps, with Kyphon ActivOs bone cement with hydroxyapatite supplied as a separate component. Alternative cements with different costs for use in kyphoplasty are available.

Percutaneous balloon kyphoplasty with stenting

- 3.5 Kyphoplasty with stenting involves inserting a small balloon catheter surrounded by a metal stent into the vertebral body using radiographic guidance and either local or general anaesthesia. The balloon catheter is inflated with liquid under pressure to create a space into which the stent is expanded. The balloon catheter is deflated and withdrawn, but the stent remains in the vertebral cavity into which high-viscosity polymethylmethacrylate bone cement is then injected. The stent's function is to prevent the vertebra from losing height after the balloon is deflated.
- 3.6 The available vertebral body stenting system (Synthes) consists of a stent catheter, an inflation system, an access kit and a balloon catheter if needed. The manufacturer stated that there is limited clinical evidence available for vertebral body stenting because it has become available only recently. Therefore, balloon kyphoplasty with stenting was not assessed in this appraisal.

Adverse reactions

- 3.7 For both vertebroplasty and kyphoplasty, adverse reactions can be caused by: needle insertion (such as local or systemic infection, bleeding and damage to neural or other structures); leakage of bone cement; displacement of bone marrow and other material by the cement; systemic reactions to the cement (such as hypotension and death); and complications related to anaesthesia and patient positioning (such as additional fractures of a rib or the sternum). In addition, there is a small risk that the balloon can rupture in kyphoplasty, which can result in the retention of balloon fragments within the vertebral body.

4 Evidence and interpretation

The Appraisal Committee considered evidence from several sources.

4.1 Clinical effectiveness

- 4.1.1 The Assessment Group carried out a systematic review and identified 9 randomised controlled trials that met the inclusion criteria. The Assessment Group adopted the term 'optimal pain management' to encompass comparator treatments in the trials that consisted of optimising pain medication while treating conservatively, or managing without surgery. Two trials (Buchbinder et al. 2009, n=78; INVEST, n=131) compared vertebroplasty with an operative placebo, which included local anaesthetic. Five trials (Farrokhi et al. 2011, n=82; VERTOS, n=46; VERTOS II, n=202; Blasco et al. 2012, n=125; Rousing et al. 2009, n=50) compared vertebroplasty with optimal pain management. One trial (FREE, n=300) compared kyphoplasty with optimal pain management and another study (Liu et al. 2010, n=100) compared vertebroplasty with kyphoplasty.
- 4.1.2 The Assessment Group highlighted that, of the randomised controlled trials, only the Buchbinder and INVEST studies were double blind. In addition, the FREE study included less than 80% of randomised patients in its final analysis and had an imbalance in drop-outs by treatment arm. The quality of the studies comparing vertebroplasty with optimal pain management (Blasco, Farrokhi, Rousing, VERTOS, and VERTOS II) varied, with the Farrokhi study being least at risk of bias. The Blasco and VERTOS II trials had substantial numbers of patients crossing over (changing treatment arms). The only study to compare vertebroplasty with kyphoplasty (Liu) was poorly reported, potentially biased and probably underpowered for its primary end point, as were the other studies, except for the Blasco, FREE, and INVEST trials. The Assessment Group stated that, in the absence of a statistically significant treatment effect in underpowered studies, it should not be assumed that no such difference exists.

Percutaneous vertebroplasty compared with operative placebo with injected local anaesthesia

- 4.1.3 The outcomes of the Buchbinder and INVEST studies included pain measured on either a numeric rating scale or a visual analogue scale (VAS). The Buchbinder study reported no statistically significant differences in the change from baseline between vertebroplasty and operative placebo with injected local anaesthesia at 1 week, or at 1, 3 or 6 months for the primary outcome of overall pain, with a mean difference adjusted for stratification variables and baselines values of 0.7 (95% confidence interval [CI] -0.4 to 1.8) at 1 week, -0.5 (95% CI -1.7 to 0.8) at 1 month, -0.6 (95% CI -1.8 to 0.7) at 3 months and -0.1 (95% CI -1.4 to 1.2) at 6 months (negative numbers indicate less severe pain). The INVEST study reported no statistically significant differences in the change in pain from baseline between groups for overall pain at 3 days, 1 week and 1 month, with an adjusted mean difference of 0.4 (95% CI -0.5 to 1.5, $p=0.37$) at 3 days, 0.1 (95% CI -0.8 to 1.1, $p=0.77$) at 1 week, and -0.7 (95% CI -1.7 to 0.3, $p=0.19$) at 1 month. The INVEST study showed a clinically meaningful improvement in pain (that is, a decrease of 30% or more) with vertebroplasty at 1 month, but this effect was not statistically significantly different from operative placebo with local anaesthesia (64% compared with 48%; $p=0.06$). In addition, the Assessment Group's meta-analysis of the individual patient data from both studies found no statistically significant improvement in change in pain from baseline between groups at 1 month, with an adjusted mean difference of -0.6 (95% CI -1.4 to 0.2). However, the number of patients taking opioids for pain decreased over time in both groups in both studies. In the Assessment Group's meta-analysis, after adjusting for baseline opioid use, patients randomised to vertebroplasty were statistically significantly more likely to be taking opioids at 1 month than patients randomised to operative placebo with local anaesthesia (relative risk [RR] 1.25, 95% CI 1.14 to 1.36, $p<0.001$). Therefore, the Assessment Group stated that the trend towards a higher proportion of patients in the vertebroplasty group achieving an improvement of 30% or more in pain scores at 1 month may have been influenced by the fact that the vertebroplasty group was more likely to be using opioids than the operative placebo with local anaesthesia group.
- 4.1.4 The Buchbinder study also reported pain as an outcome in terms of QUALEFFO (Quality of Life Questionnaire of the European Foundation for Osteoporosis) pain scores and found no statistically significant differences between groups. Data

were also collected on perceived pain, classified as 'better' or 'worse'. There were no statistically significant differences in the proportion of patients in each category at any time point. The INVEST study reported on the frequency with which patients experienced pain, and the impact of pain on their daily lives. For vertebroplasty and operative placebo with local anaesthesia, both pain frequency and pain 'bothersomeness' decreased between baseline and 1 month, with point estimates favouring vertebroplasty. However, the difference between vertebroplasty and operative placebo with local anaesthesia was not statistically significant.

4.1.5 The Buchbinder study presented health-related quality-of-life results based on AQL (Assessment of Quality of Life), EQ-5D and QUALEFFO measures. The INVEST study presented health-related quality-of-life results based on EQ-5D and SF-36. AQL scores were not different for vertebroplasty and operative placebo with local anaesthesia. EQ-5D scores, available in the Buchbinder study for 79% of patients in the vertebroplasty group and 73% in the operative placebo with local anaesthesia group, were not statistically significant different between groups for short- or medium-term outcomes. The Assessment Group's meta-analysis of individual patient data at 1 month also indicated that the result (with positive numbers indicating better quality of life) was not statistically significant (adjusted mean difference 0.03, 95% CI -0.02 to 0.08). The Assessment Group highlighted that, because 0.08 is the minimum clinically important difference for back pain on the EQ-5D scale, the confidence interval for the pooled data only just included the possibility of a clinically important difference favouring vertebroplasty. Based on QUALEFFO scores in the Buchbinder study, the only statistically significant result was at 1 week, with an adjusted mean difference of -4.0 (95% CI -7.8 to -0.2), but the Assessment Group stated that, because no minimum clinically important difference had been proposed for the QUALEFFO, the clinical significance of this result is not clear. The INVEST study found no statistically significant differences between treatment groups at any point using SF-36 scores.

4.1.6 Both the INVEST and Buchbinder studies assessed back-specific functional status using the modified 23-point version of the Roland-Morris Disability Questionnaire (RDQ). However, neither study showed any statistically significant differences for outcomes in the short-term (3 days to 2 weeks) or in the medium-term (1 month to 6 months). In addition, the Assessment Group's meta-analysis of

individual patient data from both studies indicated no statistically significant difference between treatment groups at 1 month in terms of mean RDQ scores, with an adjusted mean difference of -0.8 (95% CI -0.9 to 2.4). The INVEST study included a post hoc analysis to identify the proportion of patients who achieved a clinically meaningful (although not defined) improvement in physical disability related to back pain at 1 month. There was no difference between the proportion of patients in each group who achieved a clinically meaningful improvement (40% of the vertebroplasty group and 41% of the operative placebo with local anaesthesia group, $p=0.99$). The Assessment Group's meta-analysis also found no statistically significant difference in RDQ scores in the proportion of patients improving by at least 3 units or by at least 30%. The INVEST study reported mean Study of Osteoporotic Fractures–Activities of Daily Living (SOF-ADL) scores at baseline and 1 month, with no statistically significant difference between treatment groups in change from baseline with an adjusted mean difference of 0.4 (95% CI -0.8 to 1.6, $p=0.51$).

Percutaneous vertebroplasty compared with optimal pain management

- 4.1.7 All studies comparing vertebroplasty with optimal pain management reported pain measured on a numeric rating scale or VAS. The Farrokhi, Rousing and VERTOS II studies showed statistically significant improvements between groups in short- and medium-term changes from baseline in pain after vertebroplasty. However, the Assessment Group highlighted that the favourable result reported by Rousing at 1 month may have been unreliable because these data were collected almost a year after the event. The VERTOS II and Farrokhi studies also found statistically significant improvements in the change from baseline between groups in longer-term outcomes. However, the Assessment Group noted that in the VERTOS II study, when defining a minimum clinically important improvement as 2 or more points, the 95% confidence interval included the possibility that the results were not clinically meaningful. In the study by Blasco, statistical significance in change in pain from baseline was reported at 2 months, when the result favoured vertebroplasty.
- 4.1.8 The proportion of people taking opioids was not statistically significantly different between treatment groups in the Blasco study. However, the Assessment Group

found the results from this study difficult to interpret, partly because a higher proportion of patients in the vertebroplasty group needed opioids at baseline. In the VERTOS study, patients in the vertebroplasty group used less analgesia and patients in the control group used more analgesia, resulting in statistically significant differences that favoured vertebroplasty. In VERTOS II, analgesic use fell in the vertebroplasty group compared with the control group at 1 day ($p < 0.001$), 1 week ($p < 0.001$), and 1 month ($p = 0.033$), but not thereafter; the Assessment Group highlighted that the actual figures were not presented.

- 4.1.9 Both the Farrokhi and Blasco studies reported changes in height and deformity of the vertebral body, but the results cannot be compared because it is not clear whether the studies measured height by the same methods. The Blasco study showed no statistically significant or clinically important differences between treatment groups in the change in vertebral body height from baseline at 12 months. In contrast, the Farrokhi study showed that vertebroplasty statistically significantly improved mean vertebral body height throughout the first year but not thereafter, and statistically significantly improved and sustained angular deformity throughout the 36-month follow up period. The VERTOS II study reported data relating to the progression of treated fractures during follow up. At the last follow-up (median 12.0 months, range 1 to 24 months), statistically significant moderate or severe height loss was seen in 12% of patients in the vertebroplasty group, compared with 41% of patients in the optimal pain management group ($p < 0.001$).
- 4.1.10 The Rousing study assessed health-related quality of life using the Dallas Pain Questionnaire, which evaluates the impact of chronic pain on a patient's life. Only the score for work and leisure at 3 months reached statistical significance, favouring vertebroplasty compared with optimal pain management, but the score was unadjusted for the difference in scores at baseline. Comparing changes from baseline in each group, rather than directly comparing pain scores at 2 weeks, favoured conservative management.
- 4.1.11 VERTOS II and the Rousing study reported health-related quality of life using EQ-5D. The Rousing study provided EQ-5D utility values for 58% of patients in the vertebroplasty group and 71% in the optimal pain management group. The results, with negative differences indicating a worse outcome with vertebroplasty, indicated a mean group difference of -0.085 (95% CI -0.15 to

-0.02) at 3 months and -0.169 (95% CI -0.23 to -0.11) at 12 months, compared with baseline. VERTOS II collected EQ-5D data throughout the study but reported only baseline values.

- 4.1.12 Blasco, VERTOS and VERTOS II reported health-related quality of life using QUALEFFO. Results from the Blasco trial indicated that, in the short and medium term, there was a non-statistically significant improvement in scores with vertebroplasty compared with optimal pain management at all time points. The VERTOS study found that vertebroplasty was associated with better short-term total QUALEFFO scores than optimal pain management. In VERTOS II, after adjusting for baseline differences, there was a statistically significant difference in QUALEFFO scores at 1 year that favoured vertebroplasty ($p < 0.0001$); however, actual scores were not reported. The Rousing trial reported health-related quality of life using SF-36 and showed no statistically significant differences between treatment groups at any point.
- 4.1.13 The VERTOS and VERTOS II studies used the RDQ (24-point version) to assess back-specific functional status. The VERTOS study reported that the between-group change from baseline to 2 weeks favoured vertebroplasty over optimal pain management, but the Assessment Group could not calculate the statistical significance because the study reported no measure of variability. The VERTOS II study reported a statistically significant difference that favoured vertebroplasty at 1 year compared with optimal pain management ($p < 0.0001$); however, the study did not provide the RDQ scores or indicate what difference would reflect a clinically important difference.
- 4.1.14 The Farrokhi study reported disability using a modified Oswestry Disability Index (ODI) and reported that vertebroplasty was associated with a statistically significant improvement in change from baseline at all times from 1 week to 36 months compared with optimal pain management. The Assessment Group noted that, because 4 points on the ODI is the minimum clinically important difference for back pain, these differences were clinically meaningful throughout. The Farrokhi study also noted that all 40 patients in the vertebroplasty group could walk 1 day after vertebroplasty, but only 1 of the 42 patients (2%) in the optimal pain management group could walk 1 day after optimal pain management, indicating a relative risk of 28.3 (95% CI 5.9 to 136.5, $p < 0.0001$).

4.1.15 The Rousing study reported functional outcomes using the Barthel Index, which provided data for a subset of the study population. At 12 months, the absolute score was statistically significantly better in the vertebroplasty group than in the optimal pain management group, but the difference between groups was no longer statistically significant when adjusted for differences at baseline. The Assessment Group stated that the result may indicate a ceiling effect, whereby there is little scope for vertebroplasty to improve functional outcome more than optimal pain management does. The Rousing study also reported 3 tests of physical function for a subset of the population: tandem, timed up and go, and repeated chair tests. No statistically significant differences between groups were noted at 3 or 12 months but, because the trial provided no baseline values, the change from baseline is not known.

Percutaneous vertebroplasty compared with percutaneous balloon kyphoplasty without stenting

4.1.16 The Liu study was the only study to compare vertebroplasty with kyphoplasty, and assessed pain, vertebral body height and angular deformity. It did not assess health-related quality of life. It assessed pain measured on a VAS and reported no statistically significant differences between vertebroplasty and kyphoplasty in the short or medium term, with a mean difference of -0.2 (95% CI -0.43 to 0.03) at 3 days and 0.1 (95% CI -0.28 to 0.48) at 6 months compared with baseline, with negative differences favouring vertebroplasty. However, the Assessment Group highlighted that the trial was likely to have been underpowered. For changes in vertebral body height and angular deformity, the trial reported that kyphoplasty led to statistically significantly greater improvements in both postoperative vertebral body height and angular deformity than did vertebroplasty, but the Assessment Group was not clear at what time points the study measured these outcomes.

Percutaneous balloon kyphoplasty without stenting compared with optimal pain management

4.1.17 The FREE study was the only study to compare kyphoplasty with a non-operative treatment. For assessing pain as an outcome, the FREE study used SF-36. The

results indicated that patients randomised to kyphoplasty improved more than those randomised to optimal pain management, the difference over a period of 12 months being 9.2 points (95% CI 3.9 to 14.6, $p=0.0008$). The FREE study also reported pain measured on a numeric rating scale and reported statistically significant long-term differences between groups; however, the Assessment Group noted that these differences were unlikely to reflect a clinically meaningful difference.

- 4.1.18 The FREE study reported the use of analgesics. Kyphoplasty statistically significantly reduced the need for opioid medication at 1 month and 6 months, but not at 12 months or 24 months. The Assessment Group highlighted that the FREE study did not report changes in vertebral body height, even though maintenance of vertebral body height was a secondary outcome. The study protocol stated that vertebral body height was measured only in patients having kyphoplasty, making comparison with optimal pain management impossible. The study did show a statistically significant improvement from baseline with kyphoplasty in the kyphotic angle of the fracture at 24 months, but the Assessment Group noted that the clinical significance of this result is not clear.
- 4.1.19 The FREE study used EQ-5D and SF-36 to assess health-related quality of life. Using EQ-5D, statistically significant differences in outcomes favouring kyphoplasty over optimal pain management were reported at 1, 12, and 24 months. However, the Assessment Group highlighted that, at a minimum clinically important difference for back pain of 0.08, the confidence intervals at 3, 6, 12 and 24 months included the possibility of effects that are not considered clinically important. Using the SF-36 physical component summary score, the study reported a statistically significant mean difference of 5.2 (95% CI 2.9 to 7.4, $p<0.0001$) between groups at 1 month, favouring kyphoplasty. Although the results remained statistically significant at 3 months and 6 months, the confidence intervals included the possibility of achieving a result that may not be considered clinically important and, after 6 months, there was no statistically significant difference between treatment groups. The FREE study also reported psychological wellbeing, which was assessed by the SF-36 mental component summary score, and identified no statistically significant differences between treatment groups, although the confidence intervals included the possibility of potential clinically important treatment effects favouring kyphoplasty compared with optimal pain management at time points up to 12 months.

4.1.20 The FREE study assessed back-specific functional status using the original 24-point version of the RDQ. It showed that kyphoplasty was associated with statistically significantly better outcomes compared with optimal pain management at 1 and 12 months, but not at 24 months. Moreover, at 12 months, the confidence intervals included the possibility of not achieving a clinically important outcome. The FREE study also reported that kyphoplasty was associated with a statistically significant reduction in the probability of needing walking aids at 1 month, but not at 12 months. However, the Assessment Group noted the data were not robust because of missing data. The FREE study also recorded the number of patients who reported 1 or more days of bed rest because of back pain in the previous 14 days. At 1 month, patients in the kyphoplasty group reported on average 2.9 fewer days of restricted activity than patients in the optimal pain management group (95% CI 1.3 to 4.6, $p < 0.001$), but at 12 months the difference was no longer statistically significant (1.6 days, 95% CI -0.1 to 3.3, $p = 0.07$). The actual numbers of days of restricted activity in each group were not reported.

Mortality benefit

4.1.21 The Assessment Group stated that the trials were not powered to determine differences in overall mortality, and noted that none of the studies showed any statistically significant differences in overall mortality between treatment groups. The Assessment Group also combined 12 months of mortality data from the Blasco, Rousing and VERTOS II studies comparing vertebroplasty with optimal pain management. The point estimate of the relative risk favoured vertebroplasty, but was not statistically significant (0.68; 95% CI 0.30 to 1.57, $p = 0.37$). Medtronic provided a large observational study ($n = 858,979$) based on US Medicare registry data with follow-up to 4 years, which showed a mortality benefit with vertebroplasty or kyphoplasty compared with optimal pain management in patients with vertebral compression fractures, with a hazard ratio of 0.76 (95% CI 0.75 to 0.77) for vertebroplasty and 0.56 (95% CI 0.55 to 0.57) for kyphoplasty, adjusting for age, sex, race, Charlson comorbidity index and other coexisting diseases. In addition, kyphoplasty was associated with a greater mortality benefit compared with vertebroplasty, with an adjusted hazard ratio of 0.77 (95% CI 0.75 to 0.78; Edidin 2011). The Assessment Group stated that academic-in-confidence data provided by Medtronic on mortality at 5 years from US Medicare registry

data, as well as data from a smaller observational study (n=3,607) based on a German health insurance fund, further supported a benefit in mortality associated with the technologies. The Assessment Group stated that, apart from the possibility of uncontrolled confounding, these studies raise the possibility that improvement in biomechanical factors after treatment improves survival.

Adverse events

- 4.1.22 The Assessment Group presented adverse events reported in the trials supplemented with observational studies and case reports.
- 4.1.23 All but the Liu and INVEST studies reported cement leaks confirmed by imaging, and all had used polymethylmethacrylate cement, presumed by the Assessment Group to be of low viscosity. The Blasco study found that cement leaks did not cause patients immediate complications. However, leaks into the inferior intervertebral disc increased the risk of incident vertebral fracture (odds ratio [OR] 7.2, 95% CI 1.7 to 69.3). The Farrokhi study reported 13 asymptomatic leaks and 1 symptomatic leak into the epidural space treated with urgent bilateral laminectomy. The Rousing study stated that none of the cement leaks caused neurological symptoms. In the VERTOS II study, most leaks were discal or into segmental veins, and cement pulmonary emboli were visible on computed tomography scan in 26% (95% CI 16% to 39%) of patients, although the patients did not have symptoms. In the FREE study, most leaks went into the vertebral end-plates or they were intervertebral disc leaks, with 1 leak into the vertebral foramina, no leaks into the spinal canal, and no cement emboli.
- 4.1.24 The Buchbinder, FREE and VERTOS II studies reported postoperative infections potentially related to treatment. In the Buchbinder study, investigators administered the intravenous antibiotic cephalothin prophylactically after cement injection. Osteomyelitis developed in a patient who did not receive an antibiotic because of allergies. In the FREE study, a patient developed spondylitis in the vertebral body 376 days after surgery. Sepsis or septic shock was reported in 1 patient in the kyphoplasty group and in 3 patients in the optimal pain management group. The Assessment Group also noted that 3 patients who underwent kyphoplasty subsequently had pulmonary emboli of venous origin, and the earliest of these occurred 46 days postoperatively. The Farrokhi study

reported that no infections occurred, and the Rousing study reported that there were no adverse reactions other than cement leaks. In the remaining 4 studies (Blasco, INVEST, Liu, VERTOS), no postoperative infections were mentioned.

- 4.1.25 The risk of fracturing a vertebra adjacent to the treated vertebra was reported in 4 studies (Buchbinder, Farrokhi, FREE, Rousing), and none identified a statistically significant difference between treatment groups in the proportion of patients who experienced at least 1 clinically important fracture. However, the Blasco study noted that more (71%) of the radiographic fractures in the vertebroplasty group were clinically important compared with fewer (9%) in the optimal pain management group (OR 25.7, 95% CI 3.0 to 216.8, $p=0.029$); the investigators did not report the number of patients who had incident vertebral fractures.
- 4.1.26 The Assessment Group highlighted the potentially serious complications that can result from managing compression fractures conservatively. Bed rest can result in muscle wasting, deconditioning, deep vein thrombosis and pulmonary emboli. Opioid analgesics can cause undesirable adverse reactions including cognitive impairment, constipation and nausea, and non-steroidal anti-inflammatory drugs are associated with gastrointestinal and renal problems.

Subgroups

- 4.1.27 The Assessment Group stated that no trial data were identified for patients with or without fracture-related vertebral deformity or for inpatients at the time of randomisation. However, some data were available for subgroups based on the severity of pain at randomisation and for the time from fracture to intervention. No data for subgroups were available for kyphoplasty.
- 4.1.28 A meta-analysis by Staples et al. (2011) of individual patient data from the Buchbinder and INVEST studies grouped by baseline pain severity showed no statistically significant differences in RDQ scores, EQ-5D scores, or pain scores between patients with severe pain (score of 8 or more on a 0 to 10 scale) or mild-to-moderate pain (score of less than 8) at baseline. In both groups (vertebroplasty and operative placebo with local anaesthesia), patients with greater degrees of pain at baseline experienced a greater reduction in pain. The Assessment Group stated that this could reflect a greater potential for

improvement. The Assessment Group also stated there were no data to suggest that outcomes would differ between patients who were or were not inpatients before treatment.

- 4.1.29 The INVEST study reported results by duration of pain at baseline in post hoc analyses and found no statistically significant difference between vertebroplasty and operative placebo with local anaesthesia on pain at 1 month, but was underpowered for this analysis. Data from the Staples study combining individual patient data from the INVEST and Buchbinder studies assessed the effectiveness of vertebroplasty in patients with fracture pain of recent onset (6 weeks or less) compared with pain of longer duration. Because the INVEST study allowed crossover after 1 month, the outcomes were compared up to that time point, finding no statistically significant differences in RDQ scores, EQ-5D scores, or pain scores.

4.2 Cost effectiveness

- 4.2.1 The Assessment Group conducted a literature review that identified 1 Markov cohort model comparing the cost effectiveness of kyphoplasty with optimal pain management in patients hospitalised in the UK with vertebral compression fractures (Strom et al. 2010). The model simulated the experiences of patients until death or 100 years, with EQ-5D scores taken from the FREE study. The model assumed that the intervention would affect EQ-5D scores up to 3 years after kyphoplasty or optimal pain management, declining linearly between 1 and 3 years. The model incorporated increased risks of future vertebral fracture and increased risks of mortality after vertebral fracture. The base case assumed a cohort of 70-year-old women and men with a T-score of -2.5 SD (T-score is defined as the number of standard deviations from the average bone mineral density of healthy young women) and estimated that kyphoplasty would cost an additional £1,494 to obtain 0.169 quality-adjusted life years (QALYs), resulting in an incremental cost effectiveness ratio (ICER) of £8,840 per QALY gained for kyphoplasty compared with optimal pain management.

Medtronic model

- 4.2.2 Medtronic submitted a Markov tunnel model adapted from the Strom model (see [section 4.2.1](#)) to determine the cost effectiveness of kyphoplasty, vertebroplasty and optimal pain management in patients hospitalised with vertebral compression fractures. The model has a lifetime time horizon, 6-month cycles, and an NHS perspective. Costs and utilities are discounted at 3.5%. In the base case, Medtronic assumed that patients are 70 years old and have a T score of -3.0 SD, similar to patients in the FREE and VERTOS II trials. The model assumes people are either treated with kyphoplasty or an alternative, and remain in their initial treatment health state (progressing through the sub-states) until they die or experience another vertebral fracture that is treated using optimal pain management only. The manufacturer calculated the transition probabilities for further vertebral fractures from equations taking into account a patient's T score, age, number of previous fractures and, because the data were not available, the imputed ratio between the incidence of hip and vertebral fractures at each age, assuming that Swedish values (from Strom) apply to the UK. The transition probabilities to death use data from the Human Mortality Database for patients in the UK and the relative risks of mortality for people with a prior vertebral fracture (from Strom).
- 4.2.3 Medtronic took utility values for kyphoplasty and optimal pain management directly from the FREE trial, and for vertebroplasty indirectly from the VERTOS II trial, estimating values by adding the difference between vertebroplasty and optimal pain management to the scores for optimal pain management in the FREE trial. Because VERTOS II presented data on QALYs at baseline, 1 month and 12 months, Medtronic inferred the average utility across the 1-year period. Medtronic assumed that, unless a patient has a refracture, their utility will improve during the first 2 years and, thereafter, the utility in patients treated with optimal pain management will decline at the rate of the general population. For patients treated with kyphoplasty or vertebroplasty, the utility gain compared with optimal pain management declines linearly during the first year. Consequently after 3 years, unless patients have a refracture, they will have the same health utility, which declines at the same rate as the general population. The model assumes that both kyphoplasty and vertebroplasty improve survival compared with optimal pain management. The hazard ratios for death for kyphoplasty and for vertebroplasty are based on the US Medicare registry data.

Medtronic included recurrent vertebral fracture but no other adverse events in the model, citing a lack of data as the reason, although acknowledging potentially substantial consequences of adverse events.

- 4.2.4 The list price of a kyphoplasty kit is £2,600.50, and the submission also noted an average selling price of £1,900. Medtronic assumed an acquisition cost of vertebroplasty that was commercial in confidence. Medtronic updated the costs of the preparatory, operating and postoperative phases from those in the Strom study. Medtronic obtained data on the length of stay in hospital after treatment from Hospital Episode Statistics 2010 to 2011 data, and the cost per day in hospital from NHS Reference costs 2009 to 2011. The deterministic analyses gave an ICER of £2,167 per QALY gained for kyphoplasty compared with optimal pain management and £2,053 per QALY gained for vertebroplasty compared with optimal pain management. The deterministic analysis of kyphoplasty compared with vertebroplasty gave an ICER of £2,510 per QALY gained, while probabilistic analyses gave ICERs of £2,118 (kyphoplasty compared with optimal pain management), £2,100 (vertebroplasty compared with optimal pain management) and £2,174 (kyphoplasty compared with vertebroplasty) per QALY gained.
- 4.2.5 Medtronic conducted sensitivity analyses to study the impact of changing 1 variable at a time: the time horizon; the discount rate for costs and QALYs; the health utility benefit from the FREE trial; the time at which the utility gain for kyphoplasty and vertebroplasty compared with optimal pain management is offset linearly; mortality rates after a fracture; the price of vertebroplasty compared with kyphoplasty; the unit costs per day in hospital; the assumed T-score of the cohort; the age of the cohort; whether patients are treated with a bisphosphonate; and the proportion of patients who are male. The ICERs for kyphoplasty compared with optimal pain management and kyphoplasty compared with vertebroplasty remained below £15,000 per QALY gained in all instances. The assumption that vertebroplasty and kyphoplasty cause patients to live longer (greater for kyphoplasty than for vertebroplasty) was a key driver of the cost-effectiveness results and, when the manufacturer assumed no mortality benefit with either vertebroplasty or kyphoplasty, then the ICER for kyphoplasty compared with vertebroplasty was £27,340 per QALY gained. Medtronic noted that the ICERs for both vertebroplasty and kyphoplasty compared with optimal pain management remained low. The sensitivity analysis for changing the length of hospital stay after kyphoplasty also increased the ICER for kyphoplasty

compared with vertebroplasty to over £20,000 per QALY gained.

Johnson and Johnson model

- 4.2.6 Johnson and Johnson's model aimed to determine the cost effectiveness of vertebroplasty, kyphoplasty, optimal pain management and of operative placebo with local anaesthesia using a scenario analysis. The manufacturer developed a treatment-state model with a 1-year time horizon, an NHS perspective, and costs and benefits discounted at 3.5%. To estimate effectiveness measured by pain experienced by patients, Johnson and Johnson performed a network meta-analysis using VAS scores and EQ-5D data from trials. The manufacturer also performed an analysis based on a 'target population', that is, patients with fractures that occur within 3 months who are expected to benefit most from vertebroplasty or kyphoplasty.
- 4.2.7 The model has patients receiving different treatments and assigns values for pain using a VAS score before treatment and then again at 2 weeks depending on the intervention received. The model updates the treatment-dependent VAS score at 1 month, 6 months and 12 months. Johnson and Johnson used a regression analysis to describe the relationship between VAS and EQ-5D, based on data for both outcomes derived from a network meta-analysis. This relationship then allowed the manufacturer to model changes in quality of life from VAS scores that had been reported in trials at multiple time points. The Assessment Group stated that the manufacturer did not attempt in its network meta-analysis to extrapolate or interpolate data from trials that did not report VAS scores at the designated time intervals, and this could be a source of uncertainty when modelling pain scores over time. The Blasco study was published after completion of the manufacturer's systematic review. If the manufacturer had included this trial, which had similar VAS scores for vertebroplasty and optimal pain management (with both values being relatively high), the VAS scores in the model for all treatments would have increased and the relative difference between optimal pain management and both vertebroplasty and kyphoplasty would have diminished. Johnson and Johnson did model procedure-related adverse events.
- 4.2.8 Johnson and Johnson used a bottom-up costing approach based on published data from the Strom study for vertebroplasty and kyphoplasty. The manufacturer

did not model costs for optimal pain management because it assumed that all patients, including patients receiving vertebroplasty or kyphoplasty, would receive optimal pain management. The manufacturer determined costs of the preparatory, operating and postoperative phases from the Strom study adjusted for inflation to 2009 to 2010 prices. The costs for vertebroplasty varied according to the number of vertebrae needing treatment, being £1,358 for 1 vertebra, £1,784 for 2, and £1,848 for 3. Based on Dr Foster data, the estimated frequency of treating 1, 2 or 3 fractures resulted in an average weighted cost of £1,472. The Assessment Group noted that, in its submission, Johnson and Johnson stated that 11 cm³ of cement was needed to treat 2 fractures but the manufacturer's calculations assume 7 cm³ of cement. If 11 cm³ were used, the average weighted cost would increase to £1,546. The cost of the kyphoplasty kit reported in the Strom study was adjusted for inflation by the manufacturer to a 2009 to 2010 cost of £2,842.

4.2.9 Johnson and Johnson's base-case results indicated that vertebroplasty was both more effective and less costly than kyphoplasty and therefore dominated kyphoplasty. The analysis of vertebroplasty compared with optimal pain management gave an ICER of £4,392 per QALY gained and kyphoplasty compared with optimal pain management gave an ICER of £14,643 per QALY gained. The results based on patients with fractures that occur within 3 months who are expected to benefit most from vertebroplasty or kyphoplasty also indicated that vertebroplasty dominated kyphoplasty; the analysis of vertebroplasty compared with optimal pain management gave an ICER of £4,755 per QALY gained and kyphoplasty compared with optimal pain management gave an ICER of £15,006 per QALY gained. The scenario analysis including operative placebo with local (injected) anaesthesia resulted in vertebroplasty dominating operative placebo with local anaesthesia, and operative placebo with local anaesthesia dominating kyphoplasty. The comparison of optimal pain management with operative placebo with local anaesthesia gave an ICER of £4,853 per QALY gained.

4.2.10 Johnson and Johnson performed several other scenario analyses, pooling data from operative placebo with local anaesthesia with data from optimal pain management; extending the time horizon to beyond 1 year for both the base-case and target population with recent fractures; using an alternative bottom-up costing methodology and payment-by-results tariff for both the base-case and

the target population; and using direct EQ-5D values for both the base-case and target populations. Vertebroplasty dominated kyphoplasty in all scenarios. The ICER for vertebroplasty compared with optimal pain management ranged from £568 to £13,595 per QALY gained in the base case and from £2,550 to £16,497 per QALY gained in the target population.

4.2.11 Johnson and Johnson performed univariate sensitivity analyses comparing vertebroplasty with optimal pain management and vertebroplasty with kyphoplasty. The main drivers of cost effectiveness were the efficacy of the treatment (that is, the VAS score at various time points), and costs (driven by the length of stay, cost per bed day and surgical equipment costs) for both the base case and the population with recent fractures. Results from probabilistic sensitivity analyses (varying parameters simultaneously) were broadly similar to the deterministic results in the base-case analysis; vertebroplasty dominated kyphoplasty for both base-case and target-population analyses. In addition, in the base-case analysis, the probabilistic ICER for vertebroplasty compared with optimal pain management in the model estimated the ICER at £4,388 per QALY gained in the base-case analysis and £4,711 per QALY gained in the target population analysis. The model estimated the probabilistic ICER for kyphoplasty compared with optimal pain management at £14,718 per QALY gained in the base-case analysis and £15,010 per QALY gained in the target population analysis. In addition, the Assessment Group corrected an error in the manufacturer's mathematical model in which only 10% of patients receiving kyphoplasty consume operating-room resources; the Assessment Group assumed that this value was intended to be 100%.

Assessment Group model

4.2.12 The Assessment Group's model was designed to determine the cost effectiveness of vertebroplasty, kyphoplasty, optimal pain management and operative placebo with local anaesthesia. The Assessment Group presented 6 scenarios rather than a base case. The Assessment Group stated that, given the uncertainty around whether vertebroplasty or kyphoplasty prolonged life, it organised results into 3 categories based on whether:

- kyphoplasty prolongs life more than vertebroplasty, which prolongs life more

than optimal pain management

- vertebroplasty and kyphoplasty prolong life more than optimal pain management and
- vertebroplasty and kyphoplasty do not prolong life more than optimal pain management.

The Assessment Group also stated that the results differed based on whether it took EQ-5D directly from the trials (INVEST, FREE and Buchbinder) or mapped stable VAS scores (which the Assessment Group defined as VAS scores assumed to occur at 1 month after operation for vertebroplasty or kyphoplasty, and at 3 months after optimal pain management treatment) to EQ-5D. In addition, the Assessment Group produced exploratory analyses assuming the use of high-viscosity cement.

4.2.13 The model consisted of 5 health states:

- the starting state of post-osteoporotic vertebral compression fractures when patients receive kyphoplasty, vertebroplasty, operative placebo with local anaesthesia, or optimal pain management
- a state in which a patient may experience a subsequent vertebral fracture
- a state in which a patient may experience a subsequent hip fracture
- a state in which a patient may experience both a subsequent vertebral and a hip fracture and
- death.

The model allowed a patient to experience only 1 further vertebral fracture and 1 hip fracture. The Assessment Group assumed that a time horizon of 50 years reflects patients' lifetimes and the model employed 36 monthly time cycles followed by 47 yearly time cycles. The Assessment Group's rationale for the different cycle length was that different procedures may lead to different utilities in the period after a procedure, a difference more easily incorporated using monthly time cycles. Both costs and benefits were discounted at 3.5% per year. The model did not include the potential disutility

associated with anxiety about the prospect of future fractures, or the potential reduction in bone mineral density associated with prolonged bed rest.

- 4.2.14 The Assessment Group estimated transition probabilities between health states from the literature. Taking into consideration that a patient's bone density is likely to decrease over time, the Assessment Group incorporated a decrease of 0.255 SD per 5-year age group, assuming that women and men with the same T-score have the same risks of fracture. If a patient was assumed to be taking a bisphosphonate, the assumed effect on vertebral fractures was based on relative risks reported in the literature. This effect was assumed to last for 5 years, with a linear decline in effect over a 5-year period, so that the relative risk was 1 after 10 years. The risk of hip fracture or vertebral fracture was assumed to be independent of whether the patient was simulated to have a subsequent vertebral fracture or hip fracture.
- 4.2.15 The Assessment Group estimated the mortality rate associated with hip fracture from Stevenson et al. (2009) and the mortality rate associated with vertebral fracture from a UK study (Jalava et al. 2003). The model assumed that patients are more likely to die in the year in which a subsequent fracture occurs than they are thereafter. The model also assumed that the mortality rate after hip fracture must be equal to or greater than the mortality rates associated with a vertebral fracture in the age- and sex-matched general population. The mortality rate from causes other than fracture was taken from life tables from the Office for National Statistics, and the Assessment Group assumed that all patients die before they reach 101 years. When the Assessment Group assumed that patients who undergo kyphoplasty, vertebroplasty or operative placebo with local anaesthesia live longer than those who receive optimal pain management, mortality benefits were incorporated in the model for a period of 5 years in the base case. It was assumed that mortality benefits would cease immediately after 5 years. The Assessment Group assumed that the relative risks associated with treatment applied to all-cause mortality and to the mortality rate associated with vertebral fractures, but not to hip fractures.
- 4.2.16 The Assessment Group calculated the hazard ratios within the 3 scenarios used to explore the effects of mortality using US Medicare registry data provided, academic in confidence, by Medtronic. The Assessment Group did not have data

about any potential effect of operative placebo with local anaesthesia relative to optimal pain management on mortality, but assumed that the effect is half that observed for vertebroplasty because the effect of operative placebo with local anaesthesia on pain (VAS) was half that observed for vertebroplasty.

- 4.2.17 The Assessment Group assumed that utility values for all health states are a function of: sex; age; which procedure a patient undertakes; the time since the procedure; the time after which the model assumes that the utility values of patients treated with optimal pain management equals those of patients treated with an active intervention; the value of disutility after vertebral fractures that occurred more than 1 year before an intervention; and the mapping of VAS scores onto the EQ-5D. In addition, in the health states in which a patient had an additional vertebral and/or a new hip fracture, the model included a decrease in the utility value reflecting the fracture and, in the following cycles, persistent pain. The Assessment Group's model assumed that adverse events did not increase costs or disutility. However, the Assessment Group conducted a sensitivity analysis assuming that adverse effects led to QALY losses of 0.02 for kyphoplasty and vertebroplasty.
- 4.2.18 Costs within each of the health states were taken largely from the Stevenson study and adjusted for inflation to 2010 to 2011 prices using the Hospital and Community Health Services inflation indices. The Assessment Group took the cost of the high-viscosity Confidence Spinal Cement System from the Johnson and Johnson submission, although it assumed that 7 cm³ of cement was needed to treat 2 vertebral fractures, rather than 11 cm³. This gave an average cost of £1,546 per operation. The average estimated value for low-viscosity cement was £697. A clinical specialist advised the Assessment Group that approximately 15% of procedures would use high-viscosity cement or other more expensive cement types. The Assessment Group assumed that these more complex cases would add slightly over £100 to the average cost of an operation, resulting in an assumed cost of £800 per vertebroplasty procedure using low-viscosity cement. In calculating the ICERs, the Assessment Group assumed that vertebroplasty uses low-viscosity cement.
- 4.2.19 The Assessment Group adjusted the list price of £2,600.50 per kit for kyphoplasty to acknowledge that a proportion of patients would need kyphoplasty on more than 1 vertebra, which would require an additional pack of

Kyphon HV-R bone cement, priced at £62 per pack. This resulted in the average price per patient increasing to £2,639 for kyphoplasty. The Assessment Group assumed that the cost of operative placebo with local anaesthesia was equal to vertebroplasty, but varied this assumption in sensitivity analyses.

- 4.2.20 The Assessment Group took costs for all phases of vertebroplasty and kyphoplasty from Johnson and Johnson's submission, estimated to be £540 for the preparatory, £243 for the postoperative and £528 for the operating phases. The Assessment Group chose costs for length of hospital stay data from Medtronic's submission, which used hospital episode statistics data, and chose the value for cost per hospital day of £232 from the Johnson and Johnson submission, noting that this value is an underestimate. The clinical advisers to the Assessment Group stated that most procedures would be performed as day cases and that length of stay would be shorter than suggested by hospital episode statistics data.
- 4.2.21 The Assessment Group performed sensitivity analysis for each scenario, exploring the impact of changes to the following assumptions: assuming a bed day cost of £0; changing the assumed cost of equipment for operative placebo with local anaesthesia and the cost of the procedure; changing the time of convergence (the point at which the pain score in patients undergoing vertebroplasty equals the pain score in patients receiving optimal pain management); and including potential QALY losses associated with adverse events.
- 4.2.22 The Assessment Group summarised that, in scenarios in which the model assumes that patients who undergo kyphoplasty live longer than those who undergo vertebroplasty, results indicated that kyphoplasty provided the most QALYs and gave ICERs below £12,000 per QALY gained, irrespective of whether the utility gain expressed in EQ-5D had been estimated by mapping stable VAS, or measured directly in the trials and even if the cost of kyphoplasty was increased, assuming a separate kit was needed for each level. The ICER for vertebroplasty compared with optimal pain management, when utility gain was estimated directly from EQ-5D in the trials, remained below £7,000 per QALY gained, except in 1 instance when it was extendedly dominated, when treatment benefit was assumed to disappear between 12 months and 24 months and the EQ-5D data from the Buchbinder trial were used.

- 4.2.23 In scenarios in which the model assumed that patients who undergo vertebroplasty and kyphoplasty live longer (but by the same degree) than patients who receive optimal pain management, and when the model assumes that patients who receive operative placebo with local anaesthesia also live longer, but only to half the degree as vertebroplasty and kyphoplasty, results indicated that vertebroplasty dominated kyphoplasty because it effectively provided the same QALYs at a higher cost. The ICER for vertebroplasty compared with optimal pain management remained below £10,000 per QALY gained across all assumptions except for the combination of assumptions in which: operative placebo with local anaesthesia was assumed to have an identical mortality benefit to balloon kyphoplasty and vertebroplasty; operative placebo with local anaesthesia was assumed to have a lower cost than vertebroplasty; adverse events for vertebroplasty were included; and the EQ-5D data from the randomised controlled trials were used. In this instance, vertebroplasty was dominated by operative placebo with local anaesthesia. However, it was noted that, if operative placebo with local anaesthesia was not seen to be an appropriate comparator, the ICER of vertebroplasty compared with optimal pain management remained below £10,000 per QALY gained.
- 4.2.24 In the scenarios in which the model assumed that patients who undergo vertebroplasty and kyphoplasty do not live longer than patients who receive optimal pain management, the cost-effectiveness results depend on whether the utility gain is estimated by mapping, but vertebroplasty nonetheless typically provided the most QALYs, and the ICER remained below £16,000 per QALY gained. The exception to this was when the Assessment Group adopted assumptions unfavourable to vertebroplasty, such as hospitalisation stay costs set at £0, reduced cost of operative placebo with local anaesthesia, incorporating adverse events for vertebroplasty, and an earlier convergence over time of EQ-5D scores. When the model estimated utility gained directly from the Buchbinder and INVEST trials, vertebroplasty always dominated kyphoplasty. Vertebroplasty was dominated by operative placebo with local anaesthesia in some cases and had an ICER greater than £20,000 per QALY gained in other cases. If the Assessment Group did not consider operative placebo with local anaesthesia as an appropriate comparator, vertebroplasty compared with optimal pain management had an ICER greater than £20,000 per QALY gained in some cases.

- 4.2.25 The Assessment Group also conducted an exploratory analysis assuming the use of high-viscosity cement for all patients. It stated that, for the cost per QALY gained to be equal to £20,000 per QALY gained, an additional 0.037 QALYs would be needed, a value greater than the value of 0.02 discounted QALYs assumed in the sensitivity analyses. The Assessment Group stated that it was unlikely that the ICER for high-viscosity cement compared with low-viscosity cement would be lower than £20,000 per QALY gained. However, the Assessment Group stated that a patient might need another operation if there was a problem with low-viscosity cement. So the Assessment Group estimated that, if more than 25% of patients needed another procedure on the same vertebra, then a strategy of using high-viscosity cement in all patients for the first procedure would be more cost effective. The Assessment Group stated that it was unlikely that a strategy of using high-viscosity cement in all patients rather than a subset selected by the clinician would have an ICER of less than £20,000 per QALY gained.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of vertebroplasty and kyphoplasty, having considered evidence on the nature of osteoporotic vertebral compression fractures and the value placed on the benefits of vertebroplasty and kyphoplasty by people with the condition, those who represent them and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee considered the evidence presented by the patient experts and clinical specialists on the clinical symptoms associated with osteoporotic vertebral compression fractures. The Committee heard that these fractures have a debilitating impact on patients' ability to work and care for themselves, and consequently on their quality of life. The patient expert highlighted that, in addition to the physical pain caused by the fractures, loss of height and a distorted spine have a major impact on the emotional wellbeing and self-image of many patients. The Committee heard from the clinical specialists that people with osteoporotic vertebral compression fractures can experience problems with mobility, digestion and breathing, which may be linked to earlier mortality. The Committee acknowledged the debilitating impact that osteoporotic vertebral compression fractures have on patients' physical and emotional wellbeing.

4.3.3 The Committee discussed the clinical management of osteoporotic vertebral compression fractures. The Committee understood from the clinical specialists that vertebroplasty and kyphoplasty are performed by radiologists, anaesthetists or orthopaedic surgeons, some of whom are based in pain clinics, and they work with metabolic bone specialists to assess the need for intervention. The Committee heard that, initially, clinicians treat patients with optimal pain management including analgesics, particularly opioids and non-steroidal anti-inflammatory drugs, which are associated with considerable side effects in the older population. The Committee noted comments received during the consultation suggesting that 'optimal pain management', included in the Committee's preliminary recommendations, should be more specifically defined. However, the Committee considered that, because optimal pain management encompasses a broad array of treatments, and it means clinicians individualise therapies, it would be beyond the Committee's remit to define optimal pain management. The Committee heard that vertebroplasty and kyphoplasty are considered as treatment options in patients with recent vertebral fractures (proposed as 6 weeks) who have pain at the level of the fracture (confirmed by physical examination and magnetic resonance imaging) that is ongoing, severe, and does not respond to optimal pain management. The Committee heard that this was because, for many people, the severity of the pain will decline after 2 to 3 weeks and many people will be free of pain in 6 weeks, in line with the natural history of the condition. The clinical specialists stated that kyphoplasty can restore vertebral height to a greater extent than vertebroplasty, but this is possible only if the fracture has not healed. The Committee noted that comments received during the consultation expressed concerns over specifying a time interval of 6 weeks in which to undergo the procedures. The Committee discussed the comments and the impact of stipulating a specific time period. It acknowledged that 6 weeks may not be sufficient to permit an adequate trial of optimal pain management and imaging to confirm an unhealed fracture. The Committee also noted that, although clinicians advocate intervening in patients with recent fractures, a very small number of people with fractures are referred to secondary care with unhealed fractures months after the onset of pain and may benefit from the interventions. The Committee was aware that trials comprising the evidence base included patients with fractures older than 6 weeks. The Committee noted the lack of robust evidence to suggest an association between age of a fracture at the time of intervention and its effectiveness with respect to pain and mortality. The Committee considered that a key factor in determining

the timing of vertebroplasty and kyphoplasty was whether the fracture remained unhealed and whether it caused ongoing pain. Although the Committee appreciated the complexities in offering vertebroplasty and kyphoplasty too early (before natural healing has resulted in pain relief) or too late (when there is little chance of restoring vertebral height), it concluded that there were likely to be very few patients for whom these procedures were appropriate more than 12 weeks after fracture, and the appropriate timing in relation to the age of the fracture could be left for clinicians to judge.

4.3.4 The Committee considered the evidence for the clinical effectiveness of vertebroplasty and kyphoplasty compared with optimal pain management or operative placebo with local anaesthesia. The Committee was aware that only 2 of the trials were double blind and that results from these trials did not show statistically significant improvements in pain scores, back-specific functional status or health-related quality of life during the duration of the studies. The Committee was aware that the operative placebo that included local anaesthesia may itself reduce pain, and heard that clinicians may treat some patients with local anaesthesia injected into or near the affected vertebrae. However, the Committee agreed that operative placebo could not be considered established clinical practice for the majority of patients. In addition, it noted comments received during consultation indicating that this procedure would not be used to treat any progressive vertebral collapse. The Committee was aware that open-label studies showed that both vertebroplasty and kyphoplasty improved pain compared with optimal pain management. The Committee considered that the open-label trials better reflected 'real life' and included the comparator that would be used in clinical practice. The clinical specialists stated that, although results from the 2 double-blind trials had raised questions about the value of vertebroplasty and kyphoplasty, in clinical experience, both procedures improved pain and quality of life in people with severe symptoms. The Committee concluded that it could not disregard the results from the open-label trials, and was persuaded that there was sufficient evidence to conclude that vertebroplasty and kyphoplasty are more effective in reducing pain and restoring vertebral body height than optimal pain management in people with recent, painful osteoporotic vertebral compression fractures.

4.3.5 The Committee discussed whether vertebroplasty and kyphoplasty prolong life compared with optimal pain management. The Committee noted that the

Assessment Group pooled data on mortality at 12 months from 3 trials and found no statistically significant differences between vertebroplasty and optimal pain management (see [section 4.1.21](#)), but was aware that the studies were not designed to show a difference in mortality. However, the Committee noted that the point estimate for the mortality benefit was consistent with that estimated from 2 large scale epidemiological studies. Specifically, a large study based on US Medicare registry data that followed patients for up to 4 years reported a statistically significant mortality benefit with narrow confidence intervals, with both vertebroplasty and kyphoplasty compared with optimal pain management. The Committee noted these results, which were substantiated by an additional year of follow-up from the Medicare registry, as well as by mortality data from a smaller German study. The Committee was aware that the Medicare data had controlled for multiple comorbidities but that the possibility of confounding remained; that is, patients who have the intervention may be healthier, or otherwise different in a way that means they live longer than patients who do not undergo intervention. The Committee discussed that, given the magnitude of the benefit, taking into account further confounding would be likely to diminish, but would be unlikely to abolish, an effect. The Committee discussed the biological plausibility of a mortality benefit with vertebroplasty and kyphoplasty, and heard that improving vertebral height and spinal curvature could improve lung function, digestion and mobility, and consequently have a mortality benefit. The clinical specialists stated that most fractures occur in the thoracic spine making an impact on lung function a plausible effect. The Committee discussed the relationship between chronic pain and mortality, and felt that reducing pain may confer a mortality benefit. The Committee discussed the deleterious effects of analgesia, and the possibility of a beneficial effect on mortality of a reduced intake of opioids and non-steroidal anti-inflammatory drugs. The Committee concluded that it was reasonable to assume that both vertebroplasty and kyphoplasty prolong life compared with optimal pain management, but that the precise mechanism or magnitude of such a benefit in clinical practice in the NHS was uncertain.

- 4.3.6 The Committee also noted that, based on both sets of observational data, patients who had kyphoplasty lived longer than patients who had vertebroplasty (see [section 4.1.21](#)). The Committee heard that people who had kyphoplasty would, in general, be fitter than people who had vertebroplasty because kyphoplasty normally involves general anaesthesia and is a more technically

difficult procedure. However, the Committee was also aware that, in the trial comparing vertebroplasty with kyphoplasty, kyphoplasty was associated with statistically significantly greater improvements in both postoperative vertebral height and angular deformity compared with vertebroplasty. On balance, the Committee concluded that, given the degree of uncertainty, it was plausible that kyphoplasty may be associated with a greater mortality benefit than vertebroplasty, but the Committee would also consider the possibility that kyphoplasty and vertebroplasty had the same degree of mortality benefit.

- 4.3.7 The Committee noted the Assessment Group's comments that adverse reactions from vertebroplasty and kyphoplasty related primarily to cement leakage, particularly for vertebroplasty. Cement leakage was associated with pulmonary embolism, radiculopathy, and temporary or permanent motor deficits. The Committee heard that leakage could be intradiscal or intravascular, with intravascular leaks increasing the risk of cement pulmonary embolism. The Committee heard that, to reduce cement leakage and its complications, high-viscosity cements have been developed as an alternative to low-viscosity cements. The clinical specialists stated that, to reduce leakage of low-viscosity cements, the manufacturers were developing newer methods, and that problems from leakage were rare. The Committee concluded that cement leakage associated with vertebroplasty and kyphoplasty was manageable if the procedure is performed by a skilled clinician with specialised training in these procedures.
- 4.3.8 The Committee was aware that the Assessment Group presented 6 different scenarios based on different assumptions around mortality benefit and whether EQ-5D data were taken directly from trials or were mapped from stable VAS pain scores from a network meta-analysis. The Committee noted that taking EQ-5D data directly from the trials is in line with the NICE reference case and that there was no reason for moving away from this in this appraisal. The Committee concluded that including EQ-5D data directly from the trials was more appropriate.
- 4.3.9 The Committee noted that the Assessment Group presented results based on whether it used EQ-5D data from the FREE trial, the Buchbinder trial or the INVEST trial. For the Buchbinder and INVEST trials, the Assessment Group presented results in which it assumed that the pain in people who had had an

intervention declines to a level equal to that in people who had not had an intervention by 12 to 24 months or, alternatively, by 24 to 36 months after the procedure. The Committee agreed that it was not possible to choose only 1 of the trials as a source for the EQ-5D values, but that assuming a later convergence of pain scores, that is between 24 and 36 months, was more plausible.

4.3.10 The Committee discussed the ICERs for the scenarios in which kyphoplasty was assumed to prolong life more than vertebroplasty, while also considering the scenario in which kyphoplasty and vertebroplasty prolong life equally, using EQ-5D data included directly from trials and assuming a later convergence of pain scores (see sections 4.3.5, 4.3.8 and 4.3.9). The Committee acknowledged that, in both scenarios related to mortality, operative placebo with injection of local anaesthesia was extendedly dominated or dominated by vertebroplasty and kyphoplasty, and that the ICER for vertebroplasty compared with optimal pain management was below £7,000 per QALY gained. When kyphoplasty was assumed to prolong life more than vertebroplasty, the ICER for kyphoplasty compared with vertebroplasty was below £8,000 per QALY gained. When kyphoplasty and vertebroplasty were assumed to have the same mortality benefit, kyphoplasty was dominated by vertebroplasty. The Committee noted that the sensitivity analyses carried out by the Assessment Group, which included alternative assumptions on hospitalisation costs, costs of operative placebo and adverse events, changed the results as follows: when kyphoplasty was assumed to prolong life more than vertebroplasty, vertebroplasty was extendedly dominated, and the ICER for kyphoplasty compared with vertebroplasty was below £11,000 per QALY gained; and when kyphoplasty and vertebroplasty were assumed to have the same mortality benefit, the ICER for vertebroplasty was under £10,000 per QALY gained. The Committee concluded that the relative mortality benefits of kyphoplasty and vertebroplasty lie somewhere in between the 2 scenarios modelled by the Assessment Group. The Committee concluded that the ICERs established for both kyphoplasty and vertebroplasty were generally at the lower end of what is usually considered to be a cost-effective use of NHS resources.

4.3.11 The Committee noted that the Assessment Group had based the cost of vertebroplasty on the assumption that low-viscosity cement would be used in most procedures, allowing for high-viscosity cement to be used in 15% of procedures. The Committee noted that this assumption halved the cost of

vertebroplasty from £1,546 to £800 for 85% of procedures, as assumed in the model. The Committee heard that high-viscosity cements are being used increasingly in clinical practice based on concerns around cement leakage with low-viscosity cements, but that clinicians still use low-viscosity cements. The Committee considered that vertebroplasty would no longer be cost effective if high-viscosity cements were used in all vertebroplasty procedures. However, given that new methods are emerging to control leakage associated with use of low-viscosity cements, the Committee considered it unlikely that high-viscosity cements would be used in most vertebroplasty procedures. The Committee therefore based its recommendation on the assumption that clinicians would use low-viscosity cement in most procedures.

- 4.3.12 The Committee discussed whether kyphoplasty and vertebroplasty could be considered cost effective, given the uncertainty around their relative mortality benefits. The Committee noted that the ICERs presented by the Assessment Group were at the lower end of the range usually considered a cost-effective use of NHS resources, assuming that clinicians would use low-viscosity cements in most of the procedures, and discussed the debilitating impact that osteoporotic vertebral compression fractures have on people's physical and emotional wellbeing. On balance, the Committee concluded that both vertebroplasty and kyphoplasty could be considered a cost-effective use of NHS resources and should be recommended as options for treating osteoporotic vertebral compression fractures in people who have severe ongoing pain after a recent, unhealed vertebral fracture, despite optimal pain management, and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has osteoporotic vertebral compression fractures and the healthcare professional responsible for their care thinks that percutaneous vertebroplasty, or percutaneous balloon kyphoplasty without stenting, is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and

Tropical Medicine

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Professor Daniel Hochhauser

Consultant in Medical Oncology

Dr Neil Iosson

General Practitioner

Anne Joshua

Associate Director of Pharmacy, NHS Direct

Terence Lewis

Lay Member

Dr Rubin Minhas

General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Roderick Smith

Finance Director, West Kent Primary Care Trust

Cliff Snelling

Lay Member

Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

David Thomson

Lay Member

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ahmed Elsada

Technical Lead

Pall Jonsson and Raisa Sidhu

Technical Advisers

Jeremy Powell

Project Manager

7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by the School of Health and Related Research, University of Sheffield:

- 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. August 2012

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Manufacturers or sponsors, professional or specialist and patient or carer groups were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Cook Medical
- Johnson and Johnson
- Medtronic
- Stryker-Howmedica-Osteonics

Professional or specialist and patient or carer groups:

- Action on Pain
- British Association of Spinal Surgeons
- British Society of Interventional Radiology
- British Society of Skeletal Radiology
- Chartered Society of Physiotherapy

- National Osteoporosis Society
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Radiologists
- Society and College of Radiographers

Other consultees:

- Department of Health
- Welsh Government

Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service
- Healthcare Improvement Scotland

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on percutaneous vertebroplasty and percutaneous balloon kyphoplasty by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Nicola Peel, Consultant in Metabolic Bone Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, nominated by the National Osteoporosis Society – clinical specialist
- Dr Richard Whitehouse, Consultant Radiologist, Guidance and development of diagnostic and interventional musculoskeletal procedures, nominated by the British Society of Skeletal Radiology – clinical specialist
- Christine Sharp, nominated by the National Osteoporosis Society – patient expert
- Rick Tame, Helpline Nurse, nominated by the National Osteoporosis Society – patient expert

Representatives from the following manufacturers or sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Johnson and Johnson
- Medtronic
- Stryker-Howmedica-Osteonics

ISBN: 978-1-4731-0114-2