Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis

Draft protocol

21st October 2011

1. Title of the project:

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis

2. Name of TAR team and project 'lead'

School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield.

Lead: Matt Stevenson, Reader in Health Technology Assessment,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA

Address for correspondence

All correspondence should be sent to the Project Lead (Matt Stevenson, M.D.Stevenson@sheffield.ac.uk), the Systematic Reviewer (Myfanwy Lloyd Jones, m.lloydjones@sheffield.ac.uk), the Managing Director of ScHARR-TAG (Eva Kaltenthaler, e.kaltenthaler@sheffield.ac.uk) and the Project Administrator (Gill Rooney, g.rooney@sheffield.ac.uk).

3. Plain English Summary

Many people suffer from osteoporosis, a condition in which the mineral content of their bones decreases, making the bones weaker and more brittle. Primary osteoporosis is generally associated with aging, and is particularly common in postmenopausal women. Other people may develop osteoporosis secondary to certain medical conditions (eg hyperthyroidism, and malignant disease) or prolonged steroid therapy.[1]

Osteoporosis itself has no symptoms. However, bones weakened by osteoporosis can break easily, with little or no identifiable trauma. The most common osteoporosis-related fractures are vertebral compression fractures. These develop as the weakened vertebrae are compressed and distorted. Most vertebral compression fractures do not come to clinical attention, and do not appear to be associated with a significant increase in back pain.[2] However, some cause substantial pain and functional impairment; these are often termed "symptomatic" fractures. Most people who suffer symptomatic fractures can be treated successfully with conservative therapy,[3] but others have persistent pain and limited mobility,[4] and some may require hospitalisation, long-term care, or both.[5]

Percutaneous vertebroplasty is a procedure in which acrylic bone cement is injected into a fractured vertebra under radiological guidance with the aim of relieving pain and/or stabilising the fracture.[3,6] The procedure may be done under general anaesthetic, but is more often performed using conscious sedation and local anaesthesia.[6] Clinical complications following percutaneous vertebroplasty appear to be rare,[3] but can be serious, potentially including compression of the spinal cord.[6]

Percutaneous balloon kyphoplasty is a variant of vertebroplasty in which a balloon-like device is inserted into the fractured vertebra and then slowly inflated until the vertebral body is restored to its normal height or the balloon reaches its highest achievable volume. The balloon is then deflated and removed, and the ensuing cavity is filled with bone cement. Like percutaneous vertebroplasty, balloon kyphoplasty is performed under local or general anaesthesia.[7]

In 2003, NICE issued Interventional Procedure Guidance 12, which stated that percutaneous vertebroplasty may be considered for the provision of pain relief in patients with severe painful osteoporosis with loss of height and/or compression fractures of the vertebral body only if their pain is refractory to more conservative treatment.[8] Interventional Procedure Guidance 166, issued in 2006, stated that balloon kyphoplasty may be considered in patients with vertebral compression fractures whose condition is refractory to medical therapy and in whom there is continued vertebral collapse and severe pain.[9]

The aim of this review is to systematically evaluate and appraise the long-term efficacy, safety, and cost-effectiveness of percutaneous vertebroplasty and percutaneous balloon kyphoplasty in people with symptomatic osteoporotic vertebral compression fractures.

4. Decision problem

4.1 Purpose of the decision to be made

The assessment will address the question "What is the long-term efficacy, safety, and cost-effectiveness of percutaneous vertebroplasty and percutaneous balloon kyphoplasty (with or without vertebral body stenting) as a treatment for osteoporotic vertebral compression fractures?"

4.2 Clear definition of the intervention

Percutaneous vertebroplasty is a procedure in which acrylic bone cement is injected into a fractured vertebra under radiological guidance in order to relieve pain and/or stabilise the fracture.[3,6] The procedure may be done under general anaesthetic, but is more commonly performed using conscious sedation and local anaesthesia.[6]

Percutaneous balloon kyphoplasty is a variant of vertebroplasty in which a balloon-like device is inserted into the vertebral body and then slowly inflated until the vertebral body is restored to its normal height or the balloon reaches its highest achievable volume. The balloon is then deflated and removed, and the ensuing cavity is filled with bone cement. The procedure may be performed under either local or general anaesthetic.[7] Stents may be used to prevent the vertebral body from collapsing after the balloon is deflated, ensuring that the maximum vertebral height is retained.[10]

4.3 Place of interventions in the treatment pathway

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty are usually offered as a last resort to people with symptomatic vertebral compression fractures in whom alternative treatments have not been successful.[6,7]

4.6 Relevant comparators

The relevant comparators are the interventions themselves, and non-invasive management. There is no gold standard for non-invasive management: the American Academy of Orthopaedic Surgeons considers the strength of the evidence for the various non-invasive treatment options (such as physiotherapy, analgesia, and the use of anti-osteoporotic agents such as a bisphosphonate or strontium ranelate) to be generally weak to inconclusive, although they provide a recommendation of moderate strength for the short-term use of calcitonin.[11]

In addition to the comparators specified above, comparison with a sham procedure or no treatment is relevant in terms of safety outcomes, and also because percutaneous vertebroplasty or percutaneous balloon kyphoplasty have a potential role in people who cannot tolerate the relevant active comparator interventions, and for whom the only relevant alternative is therefore no treatment.

4.5 Population and relevant subgroups

The relevant population is people of any age and either gender with painful osteoporotic vertebral compression fractures. If the evidence permits, consideration will be given to subgroups defined by:

- time from fracture to the intervention
- presence of fracture-related deformity before treatment
- receipt of inpatient care before treatment.

4.6 Key factors to be addressed

The review aims to:

- evaluate the clinical effectiveness of percutaneous vertebroplasty and percutaneous balloon kyphoplasty in reducing pain and disability in people with osteoporotic vertebral compression fractures
- evaluate the adverse effect profile of percutaneous vertebroplasty and percutaneous balloon kyphoplasty
- estimate the cost effectiveness of percutaneous vertebroplasty and percutaneous balloon kyphoplasty in reducing pain and disability associated with osteoporotic vertebral compression fractures
- identify key areas for primary research
- estimate the possible overall cost of introducing percutaneous vertebroplasty and percutaneous balloon kyphoplasty for people with osteoporotic vertebral compression fractures in England and Wales.

4.7 *Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment*

It was agreed at the scoping workshop that people with malignancy-related vertebral fractures, and those with neuropathy in the absence of osteoporotic compression fractures, should not be included the scope of this appraisal.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'[12] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[13]

5.1 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

5.1.1 Electronic searches

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature pertaining to percutaneous vertebroplasty and percutaneous balloon kyphoplasty as treatments for osteoporotic compression fractures in men and women of all ages. Search strategies will be used to identify relevant studies (as specified in the inclusion criteria) and systematic reviews/meta-analyses (for the identification of additional trials). Searches will not be restricted by language or publication date, nor will they be restricted by publication type or study design, as studies which do not meet the review inclusion criteria may be important in identifying further relevant papers and current research. The proposed Medline search strategy is provided in Appendix 1. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager© software.

5.1.2 Databases

The following electronic databases will be searched from inception: Medline (Ovid); Medline in Process; CINAHL; EMBASE; EconLit; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI).

Current research registers (e.g. the NIHR CRN Portfolio, Current Controlled Trials, Clinical Trials.gov) will also be searched and relevant professional and research organisations contacted. Citation searches of key included studies will be undertaken using the SCI citation search facility.

5.2 Inclusion/exclusion criteria

5.2.1 Inclusion criteria

The inclusion criteria are as reported in sections 5.2.1.1-5.2.1.5 below. The review of clinical effectiveness will include any intervention studies which report at least one of the primary outcomes. This criterion will be relaxed for consideration of adverse events, when studies which do not report any of the primary outcomes may be included.

5.2.1.1 Population

The population will comprise people of any age and either gender with osteoporotic vertebral compression fractures. Studies which also include participants with non-osteoporotic vertebral fractures of other aetiologies (e.g. fractures associated with trauma, myeloma, or metastatic cancer) will be included if data relating to participants with osteoporotic fractures can be extracted separately.

5.2.1.2 Interventions
Percutaneous vertebroplasty or percutaneous balloon kyphoplasty.

5.2.1.3 Comparators
The comparators will be the interventions themselves, non-invasive management, a sham procedure, or no treatment.

5.2.1.4 Outcomes
5.2.1.4.1 Primary outcomes
- Pain/analgesic use
- Back-specific functional status/mobility
- Vertebral body height and angular deformity
- Progression of treated fracture
- Incidence of new vertebral fractures
- Health-related quality of life

5.2.1.4.2 Secondary outcomes
- All-cause mortality
- Symptomatic and asymptomatic leakage of cement (eg into adjacent intervertebral discs)
- Periprocedural balloon rupture
- Post-operative complications (including infection)
- Other adverse events
- Resource utilisation
- Cost utility.

5.2.1.5 Study design
For the review of clinical effectiveness, the best available level of evidence will be utilised, with priority given to randomised controlled studies, if available. However, this criterion will be relaxed for the consideration of adverse events, for which observational studies may be included.

5.2.2 Exclusion criteria
Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound in terms of either study design or the method used to assess outcomes will be excluded from the results. The following publication types will also be excluded from the analysis:
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

5.3 Data extraction strategy

Retrieved studies will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in section 5.2. Studies will be assessed for relevance first by title/abstract, and then finally by full text, excluding at each step studies which do not satisfy those criteria; abstract-only studies will be included. One reviewer will examine titles and abstracts for inclusion, and a second reviewer will check ten per cent of citations, with a kappa coefficient calculated to measure inter-rater reliability. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion/exclusion criteria. Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 2) and a second reviewer will check ten per cent of data extraction forms. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. Handling data obtained from the manufacturer's submission is detailed in Section 7.

5.4 Quality assessment strategy

The methodological quality of all studies which meet the inclusion criteria will be assessed according to criteria based on those proposed by Ploeg et al for the assessment of studies of percutaneous vertebroplasty[3] (see Appendix 3).

5.5 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e. if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using the Cochrane Collaboration ReviewManager© software (version 5.1).[14] Heterogeneity will be explored through consideration of the study populations, methods, and interventions, by visualisation of the results, and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

If the evidence permits, a network meta-analysis will be undertaken to determine efficacy. This will be populated with all identified trials involving an intervention or a comparator deemed relevant to the decision problem. Where a full network incorporating all interventions and comparators of interest cannot be constructed, indirect comparisons will be undertaken where applicable.

6 Report methods for synthesising evidence of cost-effectiveness

6.1 *Identifying and systematically reviewing published cost-effectiveness studies*

The sources detailed in section 5 will be used to identify studies of the cost effectiveness of percutaneous vertebroplasty or percutaneous balloon kyphoplasty. Stand-alone cost analyses based in the UK NHS will also be sought. Relevant studies identified and included in the manufacturer's submission will also be included. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[15] together with the Eddy checklist on mathematical modelling.[16]

6.2 Systematic literature search for other data related to cost-effectiveness

A search of the broader literature on outcomes following percutaneous vertebroplasty or percutaneous balloon kyphoplasty, or in patients eligible but where neither intervention was perfomed will be undertaken to identify the evidence base on HRQoL (i.e. health state values). The literature search will identify relevant values for appropriate health states. Primary data collection will not be undertaken.

6.3 *Assessment group economic model*

A new economic evaluation is likely to be carried out from the perspective of the UK NHS. The model structure will be determined in consultation with clinical experts. The TAR team has extensive experience and publication track-record using state transition modelling, discrete event simulation, individual patient modelling, meta-modelling, and the use of decision trees in economic evaluation and also of evaluating pharmaceuticals for the prevention of fractures.

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both cost and benefits will be discounted at 3.5% per annum.

Cost and utility data from published sources associated with osteoporotic fracture will be incorporated into the above model in order to allow the economic, as well as clinical, implications of treatment to be assessed. Ideally, evidence on the impact of these therapies on HRQoL will be available directly from the trials included within the review. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model.

The key model outputs will be the discounted incremental costs and discounted incremental quality adjusted life years gained for percutaneous vertebroplasty and the comparators in a full incremental analysis. Univariate sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. Probabilistic sensitivity analyses will be undertaken to determine how robust the results of the economic analysis are, given the current level of evidence, and to provide a more informative estimation of cost-effectiveness.

7 Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 15th February 2012. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions, and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or by developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8 Competing interests of authors

None.

9 Appendices

Appendix 1:

Draft Medline clinical effectiveness search strategy (Ovid)

1. Vertebroplasty/
2. Kyphoplasty/
3. vertebroplasty.ti,ab.
4. kyphoplasty.ti,ab.
5. bone void fill*.ti,ab.
6. injectable bone cement*.ti,ab.
7. osteoplastic procedure*.ti,ab.
8. vertebral* augmentation*.ti,ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

Medline Economics Strategy (SIGN Strategy)

1 Economics/
2 "costs and cost analysis"/
3 Cost allocation/
4 Cost-benefit analysis/
5 Cost control/
6 Cost savings/
7 Cost of illness/
8 Cost sharing/
9 "deductibles and coinsurance"/
10 Medical savings accounts/

11 Health care costs/
12 Direct service costs/
13 Drug costs/
14 Employer health costs/
15 Hospital costs/
16 Health expenditures/
17 Capital expenditures/
18 Value of life/
19 Exp economics, hospital/
20 Exp economics, medical/
21 Economics, nursing/
22 Economics, pharmaceutical/
23 Exp "fees and charges"/
24 Exp budgets/
25 (low adj cost).mp.
26 (high adj cost).mp.
27 (health?care adj cost$).mp.
28 (fiscal or funding or financial or finance).tw.
29 (cost adj estimate$).mp.
30 (cost adj variable).mp.
31 (unit adj cost$).mp.
32 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
33 Or/1-32

Appendix 2: Draft data extraction form

STUDY & DESIGN	DATA EXTRACTION	
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Study design (eg RCT, before-and-after study)	
	Publication type (ie full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group	
	T2: Control group	
	Intervention site (country)	
	Length of follow-up	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	

	Numbers included in the study	
	Numbers randomised	T1: T2:
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	
	Gender	
	Ethnicity	
	Primary or secondary osteoporosis	
	Number of vertebral fractures (mean)	
	Other relevant information	
	Were intervention and control groups comparable?	

	OUTCOMES	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	
	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	RESULTS	
	Adverse events	
	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers' comments	

Appendix 3: Draft quality assessment scale (adapted from Ploeg et al 2006[3])

Criterion	**Yes**	**No**	**Unclear**	**Not applicable**
Is a control group present? If yes:				
Was a method of randomisation performed?				
Was the treatment allocation concealed?				
Were co-interventions avoided or comparable?				
Was the outcome assessor blinded to the intervention?				
Were the outcome measures relevant?				
Was the withdrawal/drop-out rate described and acceptable?				
Was the timing of the outcome assessment comparable in both groups?				
Did the analysis include an intention-to-treat analysis?				
Were the eligibility criteria specified?				
Were the groups similar at baseline regarding the most important prognostic indicators?				
Were the index and control interventions explicitly described?				
Were adverse effects described?				
Was a short-term follow-up measurement performed?				
Was a long-term follow-up measurement performed?				
Was the sample size for each group described?				
Were point estimates presented for the primary outcome measures?				
Were measures of variability presented for the primary outcome measures?				
Was a valid questionnaire, eg concerning pain and quality of life, used?				

Appendix 4: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluation[15] together with the Eddy checklist on mathematical models employed in technology assessments.[16]

Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

Additional information that is needed by NCCHTA and NICE.

Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

Details of TAR team

Matt Stevenson
Reader in Health Technology Assessment and Technical Director of the ScHARR Technology Assessment Group
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA
Tel: 0114 222 0691
Fax: 0114 272 4095
E-mail: M.D.Stevenson@sheffield.ac.uk

Myfanwy Lloyd Jones, Senior Research Fellow,
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0698
Fax: 0114 272 4095
Email: m.lloydjones@sheffield.ac.uk

Angie Rees, Information Specialist
ScHARR, University of Sheffield, Regent Court, 30 Regent Street,
Sheffield S1 4DA
Tel: 0114 222 0725
Fax: 0114 272 4095
Email: a.rees@sheffield.ac.uk

Gill Rooney
Project Administrator
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA
Tel: 0114 222 0800
Fax: 0114 272 4095
E-mail: g.rooney@sheffield.ac.uk

Clinical Advisors

Eugene McCloskey
Professor of Adult Bone Diseases
Academic Unit of Bone Metabolism
Metabolic Bone Centre
Northern General Hospital
Herries Road
Sheffield S5 7AU

Email: e.v.mccloskey@sheffield.ac.uk

Dr Adrian Highland
Consultant Radiologist
Northern General Hospital
Herries Road
Sheffield
S5 7AU
Email: Adrian.Highland@sth.nhs.uk

Address for correspondence

All correspondence should be sent to the project lead, Matt Stevenson (M.D.Stevenson@sheffield.ac.uk), the systematic reviewer Myfanwy Lloyd Jones (m.lloydjones@sheffield.ac.uk), the managing director of ScHARR-TAG (Eva Kaltenthaler, e.kaltenthaler@sheffield.ac.uk), and the project administrator (Gill Rooney, g.rooney@sheffield.ac.uk).

Timetable/milestones

Milestone	
Draft protocol	5th October 2011
Final protocol	26th October 2011
Progress report	24th February 2012
Draft assessment report	30th April 2012
Assessment report	25th May 2012

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