**SUPPLEMENTAL DIGITAL CONTENT**

**Supplemental Material Section A: Search strategy**

PUBMED SEARCH

Search Date: 12/20/2013

Limits: Abstract, English, Humans

|  |  |  |
| --- | --- | --- |
|  | **Search code** | **Articles** |
|  | Fusion[TIAB] OR “Spinal Fusion”[MeSH] OR Arthrodesis[MeSH] | 65,181 |
|  | “Total Disc Replacement”[tw] OR “Disc Replacement”[tw] OR “Artificial Disc”[tw] OR “Artificial Discs”[tw] OR “Total Disc Replacement”[MeSH]  | 601 |
|  | #1 NOT #2 | 64,832 |
|  | lumbar[TIAB] OR "Lumbar Vertebrae"[MeSH] OR thoracolumbar[TIAB] OR Cervical[TIAB] OR Neck[TIAB] OR “Cervical Vertebrae”[MeSH] | 208,954 |
|  | #3 AND #4 | 11,017 |
|  | “bone morphogenetic” OR BMP OR BMP-2 OR BMP2 OR rBMP or rBMP-2 OR rBMP2 r-BMP or r-BMP-2 OR r-BMP2 OR rhBMP or rhBMP-2 OR rhBMP2 OR rh-BMP or rh-BMP-2 OR rh-BMP2  | 8441 |
|  | ceramic\*[TIAB] OR “Ceramics”[MeSH] OR cement\*[TIAB] OR Silicon[TIAB] OR Composite\*[TIAB] OR “calcium phosphate”[TIAB] OR “calcium phosphates”[TIAB] OR “phosphate”[TIAB] OR “phosphates”[TIAB] OR “pyrophosphate”[TIAB] OR “pyrophosphates”[TIAB] “calcium sulfate”[TIAB] OR “calcium sulfates”[TIAB] OR “calcium sulphate”[TIAB] OR “calcium sulphates”[TIAB] OR hydroxyapatite[TIAB] OR Synthetic\*[TIAB] OR PMMA[TIAB] OR polymethylmethacrylate[TIAB]  | 70,859 |
|  | “demineralized bone matrix”[TIAB] OR DBM[TIAB] OR “demineralized bone”[TIAB]  | 702 |
|  | Allograft\*[TIAB] OR “Transplantation, Homologous”[MeSH] OR “Allogenic”[TIAB] OR (“Homologous”[TIAB] AND (“graft”[TIAB] AND “bone”[TIAB])) OR “stem cell”[TIAB] OR “stem cells”[TIAB] OR “allogenic stem cell”[TIAB] OR “allogenic stem cells”[TIAB] OR “Trinity”[TIAB] OR “Osteocel”[TIAB] | 112,757 |
|  | #6 OR #7 OR #8 OR #9 | 189,233 |
|  | (“Cost” AND (“effectiveness” OR “utility” OR “minimization” OR “benefit”))[TIAB] OR “Economic”[TIAB] OR “Cost-Benefit Analysis”[MeSH] OR "Quality-Adjusted Life Years"[Mesh] OR “Quality-Adjusted Life Years”[MeSH] OR “Models, Economic”[MeSH] OR “Economic, medical”[MeSH] | 92,663 |
|  | #5 AND #10 AND #11 | 19 |
|  | (In Vitro[Publication Type] OR primate[tw] OR Case Reports[Publication Type] OR cancer[tw] OR cancers[tw] OR cancerous[tw] OR tumor[tw] OR tumors[tw] OR metastatic[tw] OR metastases[tw] OR infection[tw]) |  |
|  | #12 NOT #13 | 19 |

EMBASE SEARCH

Search Date: 12/18/2013

|  |  |  |
| --- | --- | --- |
|  | **Search code** | **Articles** |
| 1.        | 'spine fusion'/exp OR 'arthrodesis'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 16,153 |
| 2.        | 'total disc replacement'/exp OR 'disk prosthesis'/exp OR 'spine non fusion implant'/exp OR 'fracture'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 93,479 |
| 3.        | #1 NOT #2 | 13,550 |
| 4.        | 'lumbar spine'/exp OR 'lumbar disk'/exp OR 'lumbar vertebra'/exp OR 'cervical spine'/exp OR 'intervertebral disk'/exp OR 'thoracolumbar spine'/exp OR 'vertebra'/exp OR 'vertebra body'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 46,622 |
| 5.        | #3 AND #4 | 4,461 |
| 6.        | 'bone morphogenetic protein'/exp OR 'bone morphogenetic protein 2'/exp OR 'osteogenic protein 1'/exp OR 'recombinant osteogenic protein 1'/exp OR 'recombinant bone morphogenetic protein 2'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 7,864 |
| 7.        | 'ceramic prosthesis'/exp OR 'calcium phosphate ceramic'/exp OR 'bioprosthesis'/exp OR 'bone cement'/exp OR 'silicone prosthesis'/exp OR 'composite graft'/exp OR 'calcium phosphate'/exp OR 'phosphate'/exp OR 'pyrophosphate'/exp OR 'calcium sulfate'/exp OR 'hydroxyapatite'/exp OR 'poly(methyl methacrylate)'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 36,606 |
| 8.        | 'bone matrix'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 2,344 |
| 9.        | 'allograft'/exp OR 'allotransplantation'/exp OR 'allogenic bone marrow transplantation'/exp OR 'stem cell'/exp OR 'platelet derived growth factor'/exp OR 'recombinant platelet derived growth factor'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 112,959 |
| 10.    | #6 OR #7 OR #8 OR #9 | 154,897 |
| 11.    | 'health care cost'/exp OR 'cost effectiveness analysis'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'economic aspect'/exp AND [humans]/lim AND [english]/lim AND [abstracts]/lim | 393,841 |
| 12.    | #5 AND #10 AND #11 | 81 |
| 13.    | 'in vitro study'/exp OR 'primate model'/exp OR 'case report'/exp OR 'neoplasm'/exp OR 'metastasis'/exp OR 'infection'/exp | 9,563,228 |
| 14.    | #12 NOT #13 | 56 |

COCHRANE SEARCH

Search Date: 12/18/2013

ID            Search  Hits

#1           MeSH descriptor: [Spinal Fusion] explode all trees           693

#2           MeSH descriptor: [Arthrodesis] explode all trees              751

#3           #1 or #2                751

#4           MeSH descriptor: [Total Disc Replacement] explode all trees       13

#5           MeSH descriptor: [Spinal Fractures] explode all trees      578

#6           #4 or #5                591

#7           #3 not #6             713

#8           MeSH descriptor: [Lumbar Vertebrae] explode all trees 1885

#9           MeSH descriptor: [Cervical Vertebrae] explode all trees                662

#10         MeSH descriptor: [Neck] explode all trees           373

#11         #8 or #9 or #10 2858

#12         #7 and #11          437

#13         MeSH descriptor: [Bone Morphogenetic Proteins] explode all trees        121

#14         MeSH descriptor: [Bone Morphogenetic Protein 7] explode all trees       17

#15         #13 or #14           121

#16         #12 and #15        38

#17         MeSH descriptor: [Bone Cements] explode all trees        297

#18         MeSH descriptor: [Polymethyl Methacrylate] explode all trees  161

#19         MeSH descriptor: [Ceramics] explode all trees   431

#20         MeSH descriptor: [Calcium Phosphates] explode all trees             513

#21         MeSH descriptor: [Durapatite] explode all trees                251

#22         MeSH descriptor: [Polymethyl Methacrylate] explode all trees  161

#23         #17 or #18 or #19 or #20 or #21 or #22    1317

#24         MeSH descriptor: [Bone Matrix] explode all trees             125

#25         MeSH descriptor: [Transplantation, Homologous] explode all trees          1144

#26         MeSH descriptor: [Stem Cells] explode all trees 505

#27         MeSH descriptor: [Platelet Activating Factor] explode all trees   145

#28         #23 or #24 or #25 or #26 or #27 3183

#29         MeSH descriptor: [Cost-Benefit Analysis] explode all trees           14660

#30         MeSH descriptor: [Models, Economic] explode all trees 1746

#31         MeSH descriptor: [Quality-Adjusted Life Years] explode all trees               3329

#32         #29 or #30 or #31             15159

#33         #15 or #23 or #28             3289

**#34         #12 and #32 and #33       4**

**Supplemental Material Section B: Studies excluded after full text review with reason for exclusion.**

|  |  |
| --- | --- |
| **Study**  | **Reason for exclusion** |
| 1. Ackerman SJ, Mafilios MS, Polly DW, Jr. Economic evaluation of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion: an evidence-based modeling approach. Spine (Phila Pa 1976) 2002;27:S94-9.
 | Costing only, not a full economic analysis; preliminary study only. |
| 1. Bhadra AK, Raman AS, Casey AT, Crawford RJ. Single-level cervical radiculopathy: clinical outcome and cost-effectiveness of four techniques of anterior cervical discectomy and fusion and disc arthroplasty. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2009;18:232-7.
 | Costing only, not a full economic analysis. |
| 1. Cahill KS, Chi JH, Day A, Claus EB. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. JAMA 2009;302:58-66.
 | Costing only, not a full economic analysis. |
| 1. Cahill KS, Chi JH, Groff MW, McGuire K, Afendulis CC, Claus EB. Outcomes for single-level lumbar fusion: the role of bone morphogenetic protein. Spine (Phila Pa 1976) 2011;36:2354-62.
 | Costing only, not a full economic analysis. |
| 1. Carlqvist P, Dawson S, Jeppsson K, Borgman B. Demineralised bone matrix (DBM) versus iliac crest bone graft (ICBG) for lumbar spinal fusion procedures in the United Kingdom; A budget-impact analysis. Value in Health 2013;16:A558.
 | Abstract only. |
| 1. Deyo RA, Ching A, Matsen L, et al. Use of bone morphogenetic proteins in spinal fusion surgery for older adults with lumbar stenosis: Trends, complications, repeat surgery, and charges. Spine 2012;37:222-30.
 | Costing only, not a full economic analysis. |
| 1. Glassman SD, Carreon LY, Campbell MJ, et al. The perioperative cost of Infuse bone graft in posterolateral lumbar spine fusion. Spine Journal 2008;8:443-8.
 | Costing only, not a full economic analysis. |
| 1. Glassman SD, Carreon LY, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age. Spine (Phila Pa 1976) 2008;33:2843-9.
 | Costing only, not a full economic analysis. |
| 1. Guyer RD, Tromanhauser SG, Regan JJ. An economic model of one-level lumbar arthroplasty versus fusion. The spine journal : official journal of the North American Spine Society 2007;7:558-62.
 | Not a full economic analysis. Authors claim this to be a cost minimization but there is no info regarding therapeutic equivalence. Therapeutic equivalence must be referenced by the author conducting the study and should have been done prior to the cost-minimization work. |
| 1. Virk S, Sandhu HS, Khan SN. Cost effectiveness analysis of graft options in spinal fusion surgery using a Markov model. J Spinal Disord Tech 2012;25:E204-10.
 | Study compares fusion with living with chronic LBP, not fusion. |

*Critical appraisal*

The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[1](#_ENREF_1) was used to provide an initial basis for critical appraisal of included economic studies.{Ofman, 2003 #99} QHES is a sixteen 'yes' or 'no' question instrument that assesses multiple aspects of economic study design, modeling and reporting to determine internal validity (See Supplemental Digital Material). QHES was assessed prospectively[1](#_ENREF_1),[2](#_ENREF_2) for content and construct validity by the developers and has been evaluated externally as well.[3](#_ENREF_3) Components are weighted by importance (as concluded by expert health economists) to yield a score from 0 (lowest quality) to 100 (highest quality). Items that are considered most important (based on their weighting) include

* use of data from best available sources (e.g. RCT),
* statistical analysis to address random events and use of sensitivity analysis to explore model,
* use of appropriate sources and methodologies for measuring and estimating costs,
* use of valid and reliable outcomes measures
* transparent description of economic modeling used including delineation and justification of main assumptions and limitations of the model
* extent to which conclusions and recommendations were justified and based on study results.

 Some have suggested that a score of 75-100 points indicates a high quality economic study.[4](#_ENREF_4) The QHES does not provide insight into study external validity (generalizability) nor does it directly assess the validity of clinical assumptions and inputs. A study may receive a high score based on factors assessed in QHES, but ultimately may not be applicable to a broader range of clinical populations. Thus, in addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and consideration of potential sources of bias related to clinical inputs into the economic model.

Two reviewers independently applied the QHES to included studies. Discrepancies in ratings were discussed so that consensus could be reached and a final score obtained.

**Supplemental Material Section C: QHES.**

|  |  |  |
| --- | --- | --- |
| **QHES Question** | **Possible Points** | **Points awarded:** |
| **AHRQ** | **Alt** | **Carreon** | **Garrison/NHS** | **Polly** | **Angevine** |
| 1. Was the **study** **objective** presented in a clear, specific, and measurable manner?
 | 7 | **7** | 7 | 7 | 7 | 7 | 7 |
| 1. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?
 | 4 | **4** | 4 | 0 | 0 | 0 | 0 |
| 1. Were **variable estimates** used in the analysis **from the best available source** (i.e., randomized controlled trial - best, expert opinion - worst)?
 | 8 | **8** | 8 | 8 | 8 | 0 | 0 |
| 1. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?
 | 1 | **1** | 1 | 0 | 1 | 1 | 1 |
| 1. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?
 | 9 | **9** | 0 | 0 | 9 | 9 | 9 |
| 1. Was **incremental analysis** performed between alternatives for resources and costs?
 | 6 | **6** | 6 | 6 | 6 | 6 | 6 |
| 1. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?
 | 5 | **5** | 0 | 5 | 5 | 5 | 5 |
| 1. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?
 | 7 | **0** | 0 | 0 | 0 | 0 | 7 |
| 1. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?
 | 8 | **8** | 0 | 8 | 8 | 8 | 8 |
| 1. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?
 | 6 | **6** | 6 | 6 | 6 | 6 | 6 |
| 1. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?
 | 7 | **7** | 7 | 7 | 7 | 0 | 7 |
| 1. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?
 | 8 | **8** | 8 | 8 | 0 | 8 | 8 |
| 1. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?
 | 7 | **7** | 7 | 7 | 0 | 7 | 7 |
| 1. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**
 | 6 | **0** | 6 | 6 | 0 | 6 | 6 |
| 1. Were the **conclusions/recommendations** of the study justified and based on the study results?
 | 8 | **8** | 8 | 0 | 8 | 8 | 8 |
| 1. Was there a statement disclosing the **source of funding** for the study?
 | 3 | **3** | 0 | 3 | 3 | 3 | 3 |
| **TOTAL** | 100 | **87** | **68** | **71** | **68** | **74** | **88** |

**Supplemental Material Section D: Detailed abstraction tables.**

# KQ1: AHRQ (2010)[5](#_ENREF_5)

|  |  |
| --- | --- |
| **Type of economic evaluation** | Cost-utility analysis |
| **Country** | US |
| **Funding** | Government |
| **QHES** | 87/100 |
| **Objective** | To determine the incremental cost effectiveness of the of BMP for spinal fusion |
| **Model type** | Stationary Markov models (cycle length 1 week) |
| **Analytic perspective** | Payer perspective (CMS) |
| **Time horizon** | 2 years (short time horizon based on limited follow-up evidence) |
| **Outcome(s) reported** | Cost per QALY, ICERs |
| **Clinical data** |
| **Data source(s) (CoE of data source)** | RCT (Burkus et al. 2002 – pivotal trial for FDA approval of INFUSE (Medtronic)) |
| **Number of patients** **(% followed)** | N = 279 |
| **Diagnosis** | Single-level DDD and disabling symptoms of ≥ 6 months duration |
| **Interventions being compared** | Single level open ALIF with an LT-Cage device filled with either:INFUSE (absorbable collagen sponge infused with rhBMP-2) (n = 143)Autogenous ICBG (n = 136) |
| **Mean age (range)** | rhBMP-2: 43 yearsICBG: 42 years |
| **Sex (% female)** | rhBMP-2: 46%ICBG: 50% |
| **Outcome measures used in model (validated in disease population?)** | Health states:rh-BMP-2 (2 states): pre-fusion status (derived from radiographic fusion success probabilities); fusion rateICBG (4 states): pre-fusion status (derived from radiographic fusion success probabilities); fusion rate  |
| **Complications used in model** | rhBMP-2 (1 state): secondary interventionICBG (2 states): secondary intervention combined with the presence or absence of donor site pain |
| **Timeframe of outcomes included**  | 2 years |
| **Country of study** | US |
| **Type of organization** | Government research organization |
| **Cost data** |
| **Currency (type and year)** | US$ (2007) |
| **Cost source(s)** | Direct health care costs reported as Medicare payments from free publicly available sources (Note: indirect costs were excluded) |
| **Costs included in analysis** | Initial hospitalization (hospital and physician costs); secondary interventions (including hospital/outpatient surgical center and physician costs, removals, supplemental fixations and reoperations)In a separate analyses, BMP was treated as a bundled part of diagnosis-related group (DRG) payments and as a separate added payment amount. |
| **Timeframe of costs included** | 2 years |
| **Discount rate** | Not used for either costs or utilities (short time horizons cited as reason) |
| **Utilities** |
| **Utility basis** | Preoperative and 6-month unpublished SF-36 data (transformed into utilities using the Brazier et al. index)Utility for each of the 6 health states:* S1: Pre-fusion without donor site pain (utility = 0.54) (source: unpublished data).
* S2: Pre-fusion with donor site pain (utility = 0.52) (source: S1 utility reduced by 0.02)
* S3: Secondary intervention without donor site pain (utility = 0.49) (source: S1 utility reduced by 0.05)
* S4: Secondary intervention with donor site pain (utility = 0.47) (source: S3 utility reduced by 0.02)
* S5: Fusion with donor site pain (utility = 0.60) (source: S6 utility reduced by 0.02)
* S6: Fusion without donor site pain (utility = 0.62) (source: unpublished data)
 |
| **Utility basis disease-specific or general measure?** | General  |
| **Timeframe of utility measurements** | Preoperative and 6 months |
| **Population source of utility measure** | Same RCT used for clinical data |
| **Sensitivity analysis** |
| **Sensitivity analysis performed?** | YesConducted with a larger disutility value for donor site pain (0.05 vs. 0.02 in base case) and with utilities that were 25% lower and 25% higher than base case values |
| **Type of sensitivity analysis** | One-, two-, and three-way sensitivity analyses |
| **Variables evaluated in sensitivity analysis** | BMP added to costs; utilities; non-BMP costs; secondary intervention costs; HR of rates of achieving union/fusion; RR of having secondary interventions; BMP costs; probability of donor site pain in ICBG patients; disutility of health states with donor site pain |
| **Results** |
| **Base case results** | Assumes that initial hospital costs are identical in both groups (i.e., that rhBMP-2 cost was treated as a bundled part of the DRG payment system and thus incurred not additional cost)* Total cost (2 years)
	+ rhBMP-2: $31,159
	+ ICBG: $31,253
	+ Difference (favors rhBMP-2) = $94 (attributed to the lower probability of secondary intervention with rhBMP-2)
* Total QALYs
	+ rhBMP-2 1.218
	+ ICBG: 1.194
	+ Difference (favors rhBMP-2) = 0.024 (attributed to donor site pain in the ICBG group)
 |
| **Results of sensitivity analysis** | **One-way sensitivity analyses**:* In the majority of sensitivity analyses, rhBMP-2 remained the dominant strategy (see Table 53).
* If upper value of the RR for secondary interventions used:
	+ rhBMP-2 no longer the dominant strategy
	+ Associated with an increased cost of $2,153 (over ICBG) and an ICER of $89,765 per QALY gained
* If BMP treated as an added cost (mean estimate of $3000):
	+ rhBMP-2 no longer the dominant strategy
	+ Associated with an increased cost of $2,906 (over ICBG) and an ICER of $121,160 per QALY gained

**Two-way sensitivity analyses** (performed by varying utility values as done in the one-way sensitivity analysis and treating rhBMP-2 as an added cost of $3000)* In no scenario was rhBMP-2 the dominant treatment (see Table 54)
	+ Assumed cost of BMP $1000: ICER = $37,785 ($17,763–$50,557)\* per QALY gained
	+ Assumed cost of BMP $3000: ICER = $121,160 ($56,959–$162,714)\* per QALY gained
	+ Assumed cost of BMP $5000: ICER = $204,536 ($96,155–$274,870)\* per QALY gained
	+ Assumed cost of BMP $8000: ICER = $329,599 ($154,948–$443,385)\* per QALY gained
	+ The lowest ICER occurred when the disutility of donor-site pain was assumed to be larger (decrease of utility value by 0.05 versus 0.02), and was associated with a cost of $56,959 per QALY gained, with an assumed cost of BMP of $3000.

**Three-way sensitivity analyses** (level of BMP cost)* In all but one scenarios rhBMP-2 was not the dominant treatment (see Table 55) (except when rhBMP-2 cost assumed to be $1000 and a low risk ration value of 0.52 (favoring the treatment group) was used).

\*range of ICERS across sensitivity analyses excluding the lower and upper risk ratios for secondary intervention |
| **Study conclusion** | Authors recommend rhBMP-2 as a treatment strategy only when rhBMP-2 is not an added cost. The majority of one-way sensitivity analyses of the base case similarly found that rhBMP-2 was associated with lower costs and increased QALYs. However, when treated as an additional cost, rhBMP-2 was no longer recommended due to the fact that the cost-effectiveness ratio is very sensitive to cost. The relatively low increase in QALYs (0.018–0.051) coupled with the increased costs meant that the ICERs for rhBMP-2 use were high (range: $37,785 – $329,599 per QALY gained, depending on the cost of BMP and the analysis done). |
| **Comments** | * Limitations:
	+ Limited evidence base (1 RCT)
	+ Use of free publicly available cost estimates (likely not as accurate as more limited access sources)
	+ Probabilistic sensitivity analyses not performed (but unlikely to affect the interpretation of these analyses)
 |

# KQ1: Alt (2009)[6](#_ENREF_6)

|  |  |
| --- | --- |
| **Type of economic evaluation** | Cost effectiveness |
| **Country** | Germany, France, and UK |
| **Funding** | NR –Note: Volker Alt, Jorg Franke and Jean-Charles LeHuec are working as external independent consultant for Medtronic Sa`rl, Tolochenaz, Switzerland. |
| **QHES** | 68/100 |
| **Objective** | To calculate the financial impact of rhBMP-2 treatment in Germany, UK and France from a societal perspective with a two-year time horizon by taking into consideration the possible savings from reduction of secondary treatment costs and faster return-to-work to offset the upfront price compared with autogenous ICBG |
| **Model type** | NR |
| **Analytic perspective** | Societal |
| **Time horizon** | 2 years |
| **Outcome(s) reported** | Cost per second surgery avoidedCost per lost productivity |
| **Clinical data** |
| **Data source(s) (CoE of data source)** | Pooled data analysis from 1 prospective RCT (I/II) and 2 prospective nonrandomized controlled trials (II/III)The inclusion and exclusion criteria for the nonrandomized trials were identical to those for the RCT with the minor exception of not having a minimum Oswestry low back pain disability score for entry in one of the studies |
| **Number of patients** **(% followed)** | N = 679 (RCT, n = 279; nonrandomized trials, n = 400) (% f/u NR) |
| **Diagnosis** | DDD and ≤ grade 1 spondylolisthesis |
| **Interventions being compared** | Single-level open or laparoscopic lumbar fusion using:rhBMP-2 with the LT-CAGE device (n = 277)Autogenous ICBG (n = 402)RCT (open surgery):rhBMP-2: n = 143ICBG: n = 136Nonrandomized trials (laparoscopic surgery):rhBMP-2: n = 134ICBG: n = 266 |
| **Mean age (range)** | rhBMP-2: 42.9 yearsICBG: 40.8 yearsAge difference was statistically significant and thus adjusted for by covariate analysis. |
| **Sex (% female)** | NR |
| **Outcome measures used in model (validated in disease population?)** | Operating time, productivity loss (return-to-work) |
| **Complications used in model** | Secondary surgery (revision, removal, supplemental fixation, reoperations) |
| **Timeframe of outcomes included**  | 2 years |
| **Country of study** | US |
| **Type of organization** | NR |
| **Cost data** |
| **Currency (type and year)** | Euro€ (2008)UK costs in £ have been converted into € using an exchange rate of 0.79 £/€ (18 April 2008). |
| **Cost source(s)** | * Procedure costs:
	+ ICBG: country specific costs of single-level spinal fusion
	+ rhBMP-2: country specific of rhBMP-2 added to ICBG cost to determine total initial treatment cost in rhBMP-2 patients
* Operating room: NR
* Secondary surgery (revision, removal, supplemental fixation, reoperation): for each type of secondary surgery, respective costs determined by 2008 tariffs for each country
* Productivity loss: Country specific daily costs for productivity loss were estimated using national average gross wages per hour including employer-paid benefits; the estimated wage assumed an 8-h working day
 |
| **Costs included in analysis** | Initial treatment, OR, secondary surgery, productivity loss (return-to-work) |
| **Timeframe of costs included** | 2 years |
| **Discount rate** | NR |
| **Utilities** |
| **Utility basis** | None |
| **Utility basis disease-specific or general measure?** | N/A |
| **Timeframe of utility measurements** | N/A |
| **Population source of utility measure** | N/A |
| **Sensitivity analysis** |
| **Sensitivity analysis performed?** | No |
| **Goal of sensitivity analysis** | N/A |
| **Variables evaluated in sensitivity analysis** | N/A |
| **Results** |
| **Base case results** | **Germany*** Overall savings with BMP-2 compared to ICBG: 8,483€ per case
	+ Reduced operating time (0.9 hours, 403€/hour): 363€
	+ Reduced need for secondary surgery: 337€
		- Revision (difference between ICBG and BMP-2, 1.63%; cost per procedure, 4,173€): 68€
		- Removal (0.3%; 2,113€): 6€
		- Supplemental fixation (0.83%; 6,206€): 52€
		- Reoperation (5.07%; 4,173€): 212€
	+ Average prevented lost productivity (faster return to work, 43 days; average daily wage, 181€): 7,783€

**France*** Overall savings with BMP-2 compared to ICBG: 9,191€ per case
	+ Reduced operating time (0.9 hours, 1,202€/hour): 1,082€
	+ Reduced need for secondary surgery: 756€
		- Revision (difference between ICBG and BMP-2, 1.63%; cost per procedure, 9,654€): 157€
		- Removal (0.3%; 9,654€): 29€
		- Supplemental fixation (0.83%; 9,654€): 80€
		- Reoperation (5.07%; 9,654€): 489€
	+ Average prevented lost productivity (faster return to work, 43 days; average daily wage, 171€): 7,353€

**UK*** Overall savings with BMP-2 compared to ICBG: 8,567€ per case
	+ Reduced operating time (0.9 hours, 1,221€/hour): 1,099€
	+ Reduced need for secondary surgery: 416€
		- Revision (difference between ICBG and BMP-2, 1.63%; cost per procedure, 5,315€): 87€
		- Removal (0.3%; 5,315€): 16€
		- Supplemental fixation (0.83%; 5,315€): 44€
		- Reoperation (5.07%; 5,315€): 269€
	+ Average prevented lost productivity (faster return to work, 43 days; average daily wage, 164€): 7,052€

**→** The savings from productivity gain or productivity loss avoided accounted for 91.7%, 80.0% and 82.3% of the overall savings to the society in Germany, France, and UK, respectively. |
| **Results of sensitivity analysis** | N/A |
| **Study conclusion** | * In all the three countries, savings offset the upfront price of rhBMP-2, making rhBMP-2 a dominant strategy in ALIF surgery from a societal perspective
* rhBMP-2 therapy led to better clinical outcome for the patient and net cost savings for the society.
* The savings are mainly achieved by reduced productivity loss due to faster return-to-work time for patients treated with rhBMP-2.
 |
| **Comments** | * Both direct (costs for index procedures, revision surgeries) and indirect (return-to-work time with productivity loss) costs included
* Difference in length of stay was not included in the cost analysis as the shorter average hospital stay reflects a US specific situation; in general, the current European health care systems require a minimum length of stay for each patient.
* Return-to-work status evaluated has limitations, e.g. not all patients may have been comparable in the nature of the work performed
 |

# KQ1: Carreon (2009)[7](#_ENREF_7)

|  |  |
| --- | --- |
| **Type of economic evaluation** | Cost effectiveness |
| **Country** | US |
| **Funding** | Corporate/industry funds received; Supported by a grant from Norton Healthcare |
| **QHES** | 71/100 |
| **Objective** | To perform a cost-utility analysis using actual cost data from a randomized clinical trial of patients over 60 years old who underwent posterolateral fusion using either rhBMP-2/ACS or iliac crest bone graft (ICBG). |
| **Model type** | Decision tree analysis |
| **Analytic perspective** | Healthcare system |
| **Time horizon** | 2 years |
| **Outcome(s) reported** | Cost (improved utility) at 2 years follow-up |
| **Clinical data** |
| **Data source(s) (CoE of data source)** | RCT (single) |
| **Number of patients** **(% followed)** | N = 106 (96.2%, N = 102/106) |
| **Diagnosis** | Stenosis, spondylolisthesis, adjacent level fusion, disc pathology, deformity, instability, post-decompression revision (first 3 diagnoses most common) |
| **Interventions being compared** | Single or multi-level decompression and instrumented posterolateral fusion with:rhBMP-2/ACS (N = 50)ICBG (N = 52) |
| **Mean age (range)** | rhBMP-2/ACS: 69.2 ± 5.5 years (range NR)ICBG: 69.9 ± 5.8 years (range NR) |
| **Sex (% female)** | rhBMP-2/ACS: 70.0%ICBG: 67.3% |
| **Outcome measures used in model (validated in disease population?)** | Outcome measures included insofar as they affect cost: * whether patient was “better” (how this was defined was not clear)

SF-36 scores used to determine utility values |
| **Complications used in model**  | Complications included insofar as they affect cost:Cardiac, wound infection, gastrointestinal, urinary, neurologic deficit, other (toe fracture, shingles, IV line sepsis), persistent symptoms requiring additional interventions, nonunion on CT scan, revision surgery |
| **Timeframe of outcomes included**  | 2 years |
| **Country of study** | US |
| **Type of organization** | Spine specialty clinic |
| **Costs** |
| **Currency (type and year)** | US$ (year NR) |
| **Cost source(s)** | Direct costs (coder funded by Norton Healthcare; Medicare fee schedulewas used to assign cost or reimbursement for payments that could not be determined ) |
| **Costs included in analysis** | Note that analysis based on costs (rather than charges), and included actual reimbursements for all available hospital and physician components.Costs used in analysis: Total costs; inpatient hospital costs (operating room costs, implant costs, hospital level of service (ICU/TCU/floor), therapist visits, pharmacy costs, and radiology costs); inpatient physician services; outpatient facility costs (inpatient rehabilitation costs and any post-discharge emergency room visitsor readmissions); outpatient physician services; total payer expenditure |
| **Timeframe of costs included** | In-hospital up to 2 years post-surgery |
| **Discount rate** | Costs not discounted (authors cite 2-year study period as reason) |
| **Utility** |
| **Utility basis** | SF-36/ SF-6D (Brazier method, which estimates utility via SF-6D classification system, which consists of 6 health dimensions) |
| **Utility basis disease-specific or general measure?** | General  |
| **Timeframe of utility measurements** | 2 years |
| **Population source of utility measure** | Same RCT used for clinical data |
| **Sensitivity analysis** |
| **Sensitivity analysis performed?** | No |
| **Type of sensitivity analysis** | N/A |
| **Variables evaluated in sensitivity analysis** | N/A |
| **Results** |
| **Base case results** | * **Total cost (mean improvement in SF-6D) (2 years)** (per patient) (excludes costs of complications and additional spine treatments)
	+ rhBMP-2/ACS: $39, 967 (0.11)
	+ ICBG: $42,286 (0.10)
	+ Difference = $2319 (0.01)
* Maximum cumulative mean cost (and utility) if complications require additional treatment and revision
	+ rhBMP-2/ACS: $100,164 (0.08)
	+ ICBG: $97, 868 (0.05)
	+ Difference = $2296 (0.03)

**Costs reported, mean (range)*** Treatment (total 2 year cost) (excludes complications and additional spine treatment costs)
	+ rhBMP-2/ACS: $36,530 ($21,955–$109,027)
	+ ICBG: $34,235 ($19,988–$139,583
* Major complications: $10,888 ($2367–$47,289)
* Additional treatment for spine-related events: $5892 ($1137–$10,279)
* Revision surgery for nonunion: $46,852 ($19,408–$97,242)
 |
| **Results of sensitivity analysis** | N/A |
| **Study conclusion** | * In patients over 60 years of age, posterolateral fusion with rhBMP-2/ACS was more cost-effective than that with ICBG.
* Patients who received ICBG had more complications, increased need for additional treatment and revision surgery compared with rhBMP-2/ACS. This may account for higher costs and lower improvements in utility seen in patients receiving ICBG compared with rhBMP-2/ACS in this study population.
 |
| **Comments** | * Assumption: single payer model
* Small sample size – potentially influences observed complication rates
* Only patients > 60 years included (limits external validity)
* Does not include direct non-health costs (e.g. travel to and from healthcare provider, hiring of care-takers) and indirect costs (e.g. time off work)
* Short-term follow-up (2 years)
* RCT not specifically designed as a cost-effectiveness study
 |

# KQ1: Garrison, National Health Services (NHS) HTA (2007)[8](#_ENREF_8" \o "Garrison, 2007 #22)

|  |  |  |
| --- | --- | --- |
|  | **Original ABACUS model (2005/2006)**  | **Modified ABACUS model** |
| **Type of economic evaluation** | Cost effectiveness (or just costing?) | Cost-utility |
| **Country** | UK | same |
| **Funding** | ABACUS International sent the NHS (UK) the cost-effectiveness mode (2005). The model was funded by Medtronic.The report was conducted by the Health Technology Assessment (HTA) programme/National Institute for Health Research (NIHR); one author has been involved in a trial of BMP for Wyeth, otherwise members of the review team have no economic relationship with sponsors | Same(Modified ABACUS model received in 2006). |
| **QHES** | n/a | 68/100 |
| **Objective** | To assess the clinical effectiveness and cost-effectiveness of bone morphogenetic protein (BMP) for the treatment of spinal fusions compared with the current standards of care. | same |
| **Model type** |  |  |
| **Analytic perspective** | NR, but appears to be from payer perspective | same |
| **Time horizon** | 2 years | same |
| **Outcome(s) reported** | Cost per reduced revision  | Cost per QALY |
| **Clinical data** |  |
| **Data source(s) (CoE of data source)** | Integrated analysis including: 1 published RCT and 2 unpublished nonrandomized studies (same data as AHRQ) | Single RCT (same data as AHRQ) |
| **Number of patients** **(% followed)** | N = 679 (N = 279 from RCT; N = 400 from nonrandomized studies) | N = 279 |
| **Diagnosis** | NR | Single-level DDD and disabling symptoms of ≥ 6 months duration |
| **Interventions being compared** | Anterior open (RCT) or laparoscopic (cohort studies) spinal fusion using:INFUSE (rhBMP-2) (n = NR)Autogenous ICBG (n = NR) | Single level open ALIF with an LT-Cage device filled with either:INFUSE (rhBMP-2) (n = 143)Autogenous ICBG (n = 136) |
| **Mean age (range)** | NR | rhBMP-2: 43 yearsICBG: 42 years |
| **Sex (% female)** | NR | rhBMP-2: 46%ICBG: 50% |
| **Outcome measures used in model (validated in disease population?)** | For both open and laparoscopic:Surgery parameters (operating time, hospital stay), preoperative work status, postoperative work status, time to return to work, fusion rate | Surgery parameters (operating time, hospital stay), re-surgery rates (revision, removal, supplemental fixation, reoperation), time to return to work, fusion rate |
| **Complications used in model** | For both open and laparoscopic:re-surgery rates (revision, removal, supplemental fixation, reoperation),  | re-surgery rates (revision, removal, supplemental fixation, reoperation) |
| **Timeframe of outcomes included**  | 2 years | 2 years |
| **Country of study** | US | US |
| **Type of organization** | NR | NR |
| **Costs** |  |
| **Currency (type and year)** | UK£ (year NR) | UK£ (year NR); state that costs were updated |
| **Cost source(s)** | Unit costs from various sources:* Cost of open spinal fusion surgery: National Tariff 05-06 HRG Code
* Cost of laparoscopic fusion procedure: National Tariff 05-06 HRG Code
* Cost of BMP: Wyeth Pharmaceuticals
* Cost per hour of operating time: Rivero Arias et al 2005
* Cost per bed day: Personal Social Services Research Unit 2002; inflated to 2004 costs using the Hospital and Community Health Services Pay and Price Inflation Indices
* Cost per revision: not described in model
* Cost per removal: not described in model
* Cost per supplemental fixation: not described in model
* Cost per reoperation: not described in model
* Average sickness pay per day: Office of National Statistics, Patterns of Pay, results of the 2003 New Earnings Survery
 | Unit costs from various sources:* Cost of initial current treatment (decompression and fusion): National Schedule of Reference Costs 2005
* Cost of BMP (InductOs 12 mg Implant kit): Wyeth Pharmaceuticals
* Cost of revision spinal procedures: National Schedule of Reference Costs 2004/2005, NHS Trust, TELIP, R09
* Cost per hour of operating time: Rivero-Arias et al 2005
* Cost per bed day: National Tariff 2006/2007, R03
* Annual mean gross salary for all employee jobs, UK 2005: National Statistics UK
 |
| **Costs included in analysis** | See above list (in cost sources) | Same |
| **Timeframe of costs included** | 2 years | Same |
| **Discount rate** | Cost not discounted (due to the short time horizon) | Same |
| **Utilities** |  |
| **Utility basis** | Unpublished SF-36 data from integrated analysis above (transformed into utilities using the Brazier et al. index) | Same |
| **Utility basis disease-specific or general measure?** | General | Same |
| **Timeframe of utility measurements** | 2 years | Same |
| **Population source of utility measure** | Integrated analysis as above | RCT (Burkus et al 2002) as above |
| **Sensitivity analysis** |  |
| **Sensitivity analysis performed?** | No | No |
| **Type of sensitivity analysis** | N/A | N/A |
| **Variables evaluated in sensitivity analysis** | N/A | N/A |
| **Results** |  |
| **Base case results** | Original ABACUS model was a deterministic version.**Clinical outcomes/benefits of BMP for spinal fusion procedures:*** Reduced operating time (hours): 900
* Reduced length of hospital stay (days): 1143
* Reduced revision procedures: 78
* Additional successful fusions at 2 years: 51
* Additional QALYs: 56

**Costs*** Initial treatment costs (open or laparoscopic surgery): £5,930,025 for 1000 spinal fusion surgeries per year (£5930 per case)
* BMP cost: £7,720,032 (£7720 per case); increases annual cost by £1,790,007 (£1790 per case)
* Reduced operating time and hospital stay offset: £1,311,965 (£1312 per case)
* Reduced revision procedures offset: £275,617 (£276 per case)
* Incremental cost of BMP after savings above (operating time, hospital stay, revision procedures): £202,425 (£202 per case); reduced by £1,587,582 (£1588 per case) from initial incremental cost of £1,790,007 (£1790 per case)
* Reduced sickness payment: less 48,369 days which saves £4,595,055 per year
* **Thus, BMP-2 could save £4,392,630 in total (£4393 per case)**
 | Original ABACUS model modified to conduct Monte Carlo (probabilistic) simulations. (95% CI estimated by 10,000 Monte Carlo simulations)**Number of spinal fusion procedures in UK (95% CI):** 1024 (510–1553)**Clinical outcomes/benefits of BMP for spinal fusion procedures (95% CI):*** Reduced operating time (hours): 410 (178–695)
* Reduced length of hospital stay (days): 205 (-140 to 620)
* Reduced revision procedures: 7 (-64 to 84)
* Additional fusions at 2 years: 92 (46–140)
* Additional QALYs: 11 (-30 to 56)

**Costs (95% CI)*** Initial treatment costs
	+ ICBG: £5,410,656
	+ BMP: £7,243,909
	+ Difference: £1,833,253 (£913,722–£2,780,476)
* Avoided bone grafting cost offsets
	+ ICBG: NA
	+ BMP: -£477,699
	+ Difference: -£477,699 (-£922,042 to -£165,781)
* Cost of revision procedures
	+ ICBG: £603,232
	+ BMP: £573,139
	+ Difference: -£30,093 (-£420,074 to -£291,986)
* Total incremental costs to NHS
	+ ICBG: £6,013,888
	+ BMP: £7,339,349
	+ Difference: £1,325,461 (£583,547–£2,192,916)
* Thus, the cost per QALY gained with rhBMP-2 was estimated at £120,390; the probability that rhBMP is cost-effective at a willingness to pay threshold of £30,000 per QALY was 6.4% (low given the cost).
 |
| **Results of sensitivity analysis** | N/A | N/A |
| **Study conclusion** | The use of rhBMP-2 results in an annual savings over £4 million (4393 per patient) | The use of rhBMP-2 for spinal fusion is associated with higher costs compared with ICBG. |
| **Comments** | * Limitations:
	+ Little information about the models used and the way calculations were carried out
	+ Relative effect of BMP compared with ICBG may have been overestimated by using data from the 2 cohort studies (due to difference in baseline characteristic between studies)
* Inclusion of sickness payment had dramatic impact on results (societal perspective); depended on time of return to work reported by Burkus et al 2003 – huge discrepancy between this study and Burkus 2002.
* Cost per QALY was not reported
 | * Limitations:
	+ Little information about the models used and the way calculations were carried out
 |

# KQ1: Polly (2003)[9](#_ENREF_9)

|  |  |
| --- | --- |
| **Type of economic evaluation** | Cost-effectiveness |
| **Country** | US |
| **Funding** | Supported in part by Medtronic Safamor Danek, Memphis, Tenn.  |
| **QHES** | 74/100 |
| **Objective** | To compare costs of stand-alone ALIF with rhBMP-2 on an absorbable collagen sponge vs. autogenous ICBG in a tapered cylindrical cage or a threaded cortical bone dowel. In order to inform decision-makers about the total costs of BMP, an economic analysis was performed, which focused on spine care costs, rather than just the care (ie, the cost of fusion alone). |
| **Model type** | Cost-offset models1st model: hospital costs incurred only during the index hospitalization (does not take into account the fusion success rate or the cost of physician services) 2nd model: direct medical costs incurred during the index hospitalization and the subsequent 2 years (takes into account the fusion success rate, cost of physician services, costs associated with follow-up care and pseudarthrosis repair (due to index surgery failure))The models evaluated the degree to which BMP reduces medical resource use by obviating the need for autogenous iliac crest bone graft and by improving the lumbar spinal fusion success rateModels were based on data from 3 sources: clinical trial data, peer-reviewed literature, and expert opinion |
| **Analytic perspective** |  |
| **Time horizon** | 2 years |
| **Outcome(s) reported** | Cost per improved outcome |
| **Clinical data** |
| **Effectiveness data source(s) (CoE of data source)** | Based on a single RCT (LT-CAGE trial) (I/II) (for fusion success/failure) and on literature/expert opinion (all other outcomes/hospital resources/bone graft complications) |
| **Number of patients** **(% followed)** | RCT: N = 279 |
| **Diagnosis** | RCT: DDD with or without leg pain, with disc degeneration confirmed by patient history and radiographs |
| **Interventions being compared** | RCT: Single-level anterior spinal fusion surgery using rhBMP-2 (Infuse Bone Graft) (n = 143) or autogenous ICBG in a LT-CAGE (n = 136) |
| **Mean age (range)** | RCT: NR |
| **Sex (% female)** | RCT: NR |
| **Outcome measures used in model (validated in disease population?)** | Fusion success (defined as bridging trabecular bone, translational stability (≤ 3 mm), angular motion stability (≤ 5°)and the absence of radiolucent lines around >50% of the implant(s)), fusion failure (secondary spinal surgery), OR time, anesthesia time, recovery room time, need for blood transfusion, autograft extender/harvester use, length of stay, drain use, iliac crest backfill use |
| **Complications used in model** | Pain at donor site (severe and minor), minor complications at bone graft site (included infection, hematoma, wound dehiscence, and prolonged wound drainage), major complications at bone graft site (neuroma, vascular injury, herniation, and iliac crest fracture)Note: It was assumed that pain and complications at the bone graft site would be eliminated by BMP use (see Table 1) |
| **Timeframe of outcomes included**  | RCT: 2 years |
| **Country of study** | RCT: US |
| **Type of organization** | NR |
| **Costs** |
| **Currency (type and year)** | US$ (2001) |
| **Cost source(s)** | Costs were determined from various sources:* Professional fees for non-anesthesiologist physician services were based on the resource-based relative value scale in the 2001 Medicare Fee Schedule
* Professional fees for anesthesiologists were estimated from the 2001 Medicare Anesthesia Payment schedule
* Hospital facility costs were based on 1999 charge data from Solucient Incorporated's Projected Inpatient Database, the largest available all-payer inpatient database
* Cost of autograft extenders, autograft harvesters, iliac crest backfill, transcutaneous electrical nerve stimulation, and drains were obtained from the manufacturers of these products (Medtronic, Osteotech, Zimmer, Theratech)
* Cost of the operating room, anesthesia, recovery room, and room and board were obtained from a rehabilitation hospital based in the southeast United States
* Cost of inexpensive medical and surgical supplies such as gelfoam, sutures, skin staplers, bone wax, and sponges were obtained from Milliman & Robertson CareWeb Guidelines.
* Cost of medications was based on 80% of the average wholesale price listed in the *Drug Topics Red Book* (to reflect actual acquisition costs, 20% was deducted from the average wholesale price)
 |
| **Costs included in analysis** | Model 1 (index hospitalization only) costs: rhBMP-2, OR, anesthesia, recovery room stay, blood loss (transfusion), autograft extenders, autograft harvesters, LOS, drain use, iliac crest backfill useModel 2 (index hospitalization through 2 years) costs: rhBMP-2, inpatient physician services, OR, anesthesia, recovery room stay, blood loss (transfusion), LOS, autograft extenders, autograft harvesters, medical/surgical supplies, averted complications (severe pain, minor pain, infection, hematoma, would dehiscence, prolonged would drainage, vascular injury, herniation, iliac crest fracture), follow-up care (after successful index surgery, after unsuccessful index surgery but before pseudarthrosis repair, pseudarthrosis repair, after successful pseudarthrosis repair, after unsuccessful pseudarthrosis repair) |
| **Timeframe of costs included** | NR |
| **Discount rate** | Not discounted (short time horizon cited as reason) |
| **Utilities** |
| **Utility basis** | None |
| **Utility basis disease-specific or general measure?** | N/A |
| **Timeframe of utility measurements** | N/A |
| **Population source of utility measure** | N/A |
| **Sensitivity analysis** |
| **Sensitivity analysis performed?** | Yes |
| **Goal of sensitivity analysis** | To determine the consequences of alternative assumptions about the price of BMP, the fusion success rate, the time horizon of the 2-year cost model (5 years rather than 2 years), and reductions in resource use attributable to BMP use. |
| **Variables evaluated in sensitivity analysis** | Table 5* Price of BMP
* Fusion success rates
	+ Using data from a second RCT (“Bone Dowel” trial; used a threaded cortical allograft bone dowel (rhBMP-2 (n = 24) and ICBG autograft (n = 22); inclusion criteria and fusion success criteria same as RCT used for base case; 2 year follow-up)
	+ Using rates/ranges determined from clinical trial data, literature and expert opinion
* Smokers
* Pain and complication rates averted by BMP
* Operating room and anesthesia time (reduced by BMP)
* LOS (decreased by BMP)
* Use of autograft extenders/harvesters
* Time horizon 5 years rather than 2 years
* Cost of autologous vs. homologous blood and BMP reduces difference in probability of 1 unit blood transfusion by 10% rather than 5%
* Use of electrical stimulation
 |
| **Results** |
| **Base case results** | **2 years (Table 4)*** Total incremental direct medical costs of spinal fusion with rhBMP-2 and ICBG were equivalent: savings of $9 favoring (BMP base case cost $3380)
* Cost of BMP was offset by savings due to:
	+ Less inpatient physician services: $337
	+ Prevention of pain and complication associated with ICBG harvesting: $549
		- severe pain $93
		- minor pain $79
		- infection/hematoma/wound dehiscence/ prolonged wound drainage $302
		- vascular injury/herniation/iliac crest fracture $75
	+ Shorter operating room time: $540
	+ Shorter anesthesia time: $60
	+ Shorter recovery room time: $45
	+ Less blood loss: $4
	+ Short inpatient LOS: $231
	+ Autograft extenders/harvesters: $474
	+ Less medical/surgical supplies: $125
* The higher index surgery fusion success rate with BMP vs. ICBG (94.5% vs. 88.7%) contributed to the remaining cost offset for BMP ***after initial hospitalization*** by reducing costs of follow-up care, rehabilitation, and pseudarthrosis due to index surgery failure: $1024
* Overall, model indicates that the cost of BMP ($3380) during the initial inpatient stay can be recaptured over 2 years by eliminating harvest-related morbidity and other hospital costs associated with autogenous ICBG and by improving the fusion success rate.

**Index hospitalization only (excludes physician costs and follow-up care) (Table 6)*** Total incremental direct medical costs of spinal fusion were greater with BMP compared to ICBG: increased cost of $1734 with BMP (BMP base case cost $3380)
* Although the 2 treatments were no longer cost-equivalent, approximately 50% of the of the price of BMP was offset by preventing complications associated with:
	+ Iliac crest harvesting: $167
	+ Shorter operating room time: $540
	+ Shorter anesthesia time: $60
	+ Short recovery room time: $45
	+ Less blood loss: $4
	+ Shorter inpatient LOS: $231
	+ Autograft extender/harvesters: $474
	+ Medical surgical/supplies: $125

**Threshold analysis (performed determine the price at which BMP would need to be established to result in cost-neutrality, i.e. the point at which total 2-year cost for BMP patients equals total 2 year cost for autogenous ICBG)*** Fusion success rate of BMP 94.5% and ICBG 88.7% (LT-CAGE trial): cost neutrality achieved at BMP price of $3389
* Fusion success rate of BMP 100% and ICBG 68.4% (Bowel Dowel trial): cost neutrality achieved at BMP price of $7944
 |
| **Results of sensitivity analysis** | Table 5* Cost were sensitive to changes in assumptions about:
	+ Price of BMP
		- $3000 (rather than $3380):
			* 2 years: cost savings of $389 (% of BMP cost that is offset: > 100%)
			* Index hospitalization only: increased cost of $1354 (% of BMP cost that is offset: 55%)
		- $8000 (rather than $3380):
			* 2 years: increased cost of $4611 (% of BMP cost that is offset: 42%)
			* Index hospitalization only: increased cost of $6354 (% of BMP cost that is offset: 21%)
	+ Fusion success rate
		- 90% with BMP (rather than 94.5% [base case]):
			* 2 years: increased cost of $785 (% of BMP cost that is offset: 77%)
			* Index hospitalization only: N/A
		- 85% with BMP (rather than 94.5%):
			* 2 years: increased cost of $1668 (% of BMP cost that is offset: 51%)
			* Index hospitalization only: N/A
		- Bone Dowel trial fusion rates of 100% for BMP vs. 68.4% for ICBG:
			* 2 years: cost savings of $4564 (% of BMP cost that is offset: >100%)
			* Index hospitalization only: N/A
	+ Smokers (assumes a fusion rate of 90% in BMP vs. 75% in ICBG patients, as opposed to base case rates of 94.5% and 88.7%, respectively)
		- * 2 years: cost savings of $1632 (% of BMP cost that is offset: >100%)
			* Index hospitalization only: N/A
* Costs were insensitive to changes in assumptions about:
	+ Complication rates associated with bone harvesting, LOS, autograft extender/harvest use, time horizon, autologous blood use, external electrical stimulation use
 |
| **Study conclusion** | * The upfront price of BMP ($3380 in the base case) is likely to be offset to a significant extent by reductions in the use of other medical resources, particularly if costs incurred during the 2-year period following the index hospitalization are taken into account
* The major cost drivers in this analysis were (in decreasing order): price of BMP, fusion success rate, averted donor site pain and morbidity, operating room and anesthesia time, length of stay, and autograft extender use rate
* Under the base case assumptions (fusion success rates of 94.5% for rhBMP-2 and 88.7% for autogenous iliac crest bone graft; LT-CAGE clinical trial), cost-neutrality was achieved at a BMP price of $3389
* Sensitivity analyses indicate that under an alternative scenario about the fusion success rates (100% for rhBMP-2 and 68.4% for autogenous iliac crest bone graft; Bone Dowel clinical trial), cost-neutrality would be achieved over a 2-year period at a BMP price of $7944
 |
| **Comments** | * Indirect costs and nonmedical cost not considered in either model
* Fusion success rate has tremendous effect on the price at which cost-neutrality is achieved
* Models described in published papers not available electronically for detailed review
* Input estimated were heavily based on expert opinion
 |

# KQ2: Angevine (2005)[10](#_ENREF_10)

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| --- | --- |
| **Type of economic evaluation** | Cost utility |
| **Country** | US |
| **Funding** | Professional organization – (partially supported by Wilder C. Penfield Clinical Investigation Fellowship of the Congress of Neurologic Surgeons) |
| **QHES** | 88/100 |
| **Objective** | To determine the relative cost-effectiveness of anterior cervical discectomy and fusion (ACDF) with autograft, allograft, and allograft with plating for single-level anterior cervical spondylosis. |
| **Analysis** | Decision tree (perioperative period and first year post-surgery); Markov model (health status and reoperations between 1 and 5 years post-surgery) |
| **Analytic perspective** | Societal perspective |
| **Time horizon** | 5 years |
| **Outcome(s) reported** | Cost per QALY |
| **Interventions being compared** | Single-level ACDF with:* Autograft alone
* Allograft alone
* Allograft and plating (ACDFP)
 |
| **Clinical data** |
| **Data source(s) (CoE of data source)** | Effectiveness outcomes: Determined from the literature (2 cohort studies (LoE II/III) 2 case series (LoE IV)) Complications: Based on the literature (2 cohort studies (LoE II/III), 15 case series (LoE IV); 1 editorial; 1 biomechanical cadaveric study; 1 review (HIV risk)). In some cases, complication rates were determined directly from the literature; in other cases assumptions regarding complication rates were made based on one or more studies.  |
| **Number of patients** **(% followed)** | NR |
| **Diagnosis** | Cervical disc disease and spondylosis |
| **Mean age (range)** | NR (various sources) |
| **Sex (% female)** | NR (various sources) |
| **Outcome measures used in model (validated in disease population?)** | 1st year: clinical improvement, improvement after reoperation, time until return to work Long-term outcomes: symptomatic worseningHealth state utilities: preoperative, improved, not improved (see utilities below) |
| **Complications used in model** | Perioperative and 1st year: death, cord injury, root injury, reoperation other than graft or hardware complication, infection, dysphagia, chronic donor site pain, HIV from graft, graft complication, hardware complicationMarkov model (i.e., long-term complications): ASD, reoperation for ASD |
| **Timeframe of outcomes included**  | 1 year; yearly outcomes to 5 years |
| **Country of study** | NR (various sources) |
| **Type of organization** | NR (various sources) |
| **Cost data** |
| **Currency (type and year)** | US$ (2000)  |
| **Cost source(s)** | Costs were determined from the following:* a retrospective analysis of 78 patients with cervical disc disease and spondylosis (single-level ACDF with allograft alone (n = 31) or allograft and plating (ACDFP) (n = 47))
* Previously published costing studies
 |
| **Costs included in analysis** | * From the 78 patients reviewed retrospectively:
	+ Itemized hospital bills reviewed for base case costs (Charges converted to approximate costs using specific cost to charge ratios from the Institutional Cost Reports prepared for the Health Care Financing Administration.)
* From Medicare physician fee reimbursements:
	+ Cost of the surgeon’s time for each procedure
* Other costs included (source not clear):
	+ Cost of reoperation for graft or hardware complication
	+ Cost of reoperation for other complications (e.g., hematomas, deep wound infections)
	+ Cost of spinal cord injury
	+ Cost of HIV injection

Note: costs accrued after hospital discharge were not included |
| **Timeframe of costs included** | NR |
| **Discount rate** | 3% per year (for both costs and benefits in the base case analysis); this rate was varied in the sensitivity analysis from 0% to 10%. |
| **Utilities** |
| **Utility basis** | Health state utilities: preoperative (0.81), improved (1.0), not improved (0.81)Derived from a study of ACDF that reported both pre-and postoperative SF-36 scores (converted into utilities using an algorithm base on the Health Utility Index (HUI2))  |
| **Utility basis disease-specific or general measure?** | General  |
| **Timeframe of utility measurements** | NR |
| **Population source of utility measure** | Previously published case series (CoE IV) of ACDF that reported pre- and postoperative SF-36 scoresN = 28 (64% female; mean age: 44 years)Diagnosis: cervical radiculopathyTreatment: 1- or 2-level ACDFFollow-up: mean 21.8 months |
| **Sensitivity analysis** |
| **Sensitivity analysis performed?** | Yes |
| **Goal of sensitivity analysis** | Because the utility value assigned to “improved” patients was 1.0 and likely overestimates the benefits of ACDF, various utilities were tested in sensitivity analysis. |
| **Variables evaluated in sensitivity analysis** | Equal postoperative recovery periods (4 weeks), symptomatic health state utility 0.70, “improved” health state utility 0.90, maximum probability of hardware complication (0.048)/baseline probability of graft complication (0.048), baseline hardware complication rate (0.0)/maximum graft complication rate (0.087), maximum probability of hardware complication (0.048)/minimum probability of graft complication (0.0), annual probability of delayed symptomatic worsening twice baseline, discount rate |
| **Results** |
| **Base case results** | **5 years**ACDF-autograft* Cost: $11,230
* QALYs: 4.365

ACDF allograft* Cost: $11,290 (difference vs. ACDF-autograft: $60)
* QALYs: 4.486 (difference vs. ACDF-autograft: 0.121)
* ICER: $496 (vs. ACDF- autograft)

ACDFP* Cost: $12,690 (difference vs. ACDF-allograft: $1400)
* QALYs: 4.486 (difference vs. ACDF- allograft: 0.043)
* ICER: $32,560 (vs. ACDF- allograft)
 |
| **Results of sensitivity analysis** | See Tables 6-7Sensitivity analysis* Equal postoperative recovery periods (4 weeks): results in ACDFP dominating ACDF-allograft
* Variability in utilities for pre- and postoperative health states:
	+ Larger effect sizes (lower symptomatic utilities or higher asymptomatic utilities) resulted in smaller ICERs
	+ Narrower effect sizes (higher symptomatic utilities or lower asymptomatic utilities) resulted in increased ICERs
* Variability in probabilities of delayed reoperation and hardware and graft complications:
	+ ACDFP ICER: $19,090 - $60,000 (vs. ACDF- allograft)
* Discount rate: ICERS were very stable for discount rates between 0% and 10%

Two-way sensitivity analysis (ACDFP vs. ACDF-allograft)* Annual probability of delayed ASD: if recovery period was 4 weeks, ACDF-allograft dominated; if 7 weeks then ICER was $32,560
* Symptomatic worsening twice baseline: if recovery period was 4 weeks, ACDF-allograft dominated; if 7 weeks then ICER was $33,310
 |
| **Study conclusion** | * ACDF with autograft, ACDF with allograft, and ACDFP have similar cost-effectiveness ratios
* Results very sensitive to costs of procedures and to rate of postoperative recovery
* ACDF with allograft offers a benefit relative to ACDF with autograft at a cost of $496 per QALY.
* ACDFP has a benefit relative to ACDF with allograft at an approximate cost of $32,560 per QALY.
* Further research needs to be performed regarding these procedures, particularly examining the postoperative recovery period.
 |
| **Comments** | * Authors noted that there is no compelling evidence in the literature that one procedure is better than another in terms of symptom relief
* Assumptions based largely on data from case series from a wide variety of publications
* Fusion status not included in model
 |

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