NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Percutaneous Vertebroplasty (PVP) and Balloon Kyphoplasty (BKP) for the treatment of Osteoporotic Vertebral Compression Fractures (OVCFs)

Medtronic Response to ScHARR Assessment Report

13 September 2012

Executive summary

The AG should be commended for the rigour, thoroughness and clarity of their report. However, Medtronic would like to highlight some fundamental flaws which risk misleading the Appraisal Committee in their deliberations as they affect the accuracy and precision of the cost effectiveness estimates presented for the vertebral augmentation procedures, and in particular for balloon kyphoplasty:

1. The heterogenous nature of the OVCF population is not appropriately described in the report, nor are the implications recognised.
2. Failure to recognize the majority of current NHS clinical practice has led to selection of inappropriate population and therefore studies
3. Unscoped and inappopriate inclusion of comparator – Operative Placebo Local Anaesthesia (OPLA)
4. Underestimation of relative benefit of BKP
5. Innacurate acquisition cost of balloon kyphoplasty

The cost effectiveness scenario submitted by Medtronic models a cohort of *hospitalised* (proxy for disability) *acute symptomatic osteoporotic vertebral compression fractures* and uses data from sources that reflect this same cohort (FREE, VERTOS II, Medicare claims database). It is worth mentioning there's no equivalent to this scenario in the AG's report. The closest match would be scenario 2 (utility gain directly from FREE and differential beneficial effects on mortality for BKP and PVP in OVCF patients that survived first year post intervention from Medicare Claims database).

Medtronic would urge the AG to address these prior to the first Committee meeting.

Medtronic
Alleviating Pain · Restoring Health · Extending Life

1. The heterogeneous nature of the OVCF population is not appropriately described in the report, nor are the implications recognised.

Vertebral Augmentation (VA) procedures – PVP and BKP - are only appropriate for a sub-set of the scoped population. These are *acute* (≤ 6 weeks) *symptomatic* (at least VAS pain ≥ 5 correlating with fracture) vertebral compression fractures. BKP, in particular, is considered appropriate for patients who have proof of on-going fracture process[a] and spinal deformity[b] (Anselmetti 2012). These criteria are similar to the inclusion criteria used in the more recent larger RCTs on VA procedures, (FREE[1], VERTOS II[2]) and comparative non-RCT[3–5]. These criteria represent current NHS clinical practice[c]; whereby hospitalised patients are referred to spine surgeons for further examination and diagnostic work-up due to their level of disability. In general, VAS pain ≥ 5 correlating with fracture, i.e. positive MRI STIR image revealing oedema and x-ray showing vertebral collapse, deem a patient suitable for vertebral augmentation.

2. Failure to recognize the majority of current NHS clinical practice has led to selection of inappropriate population and therefore studies

The AG's failure to recognise the appropriate patient population for vertebral augmentation has led to the inclusion of inappropriate studies in its review and meta-analysis. In particular, the INVEST[6] and Buchbinder studies[7] are not consistent with the indication for the procedures under consideration as they include a significant proportion of OVCF patients who would not be considered clinically appropriate for a vertebral augmentation procedure in the NHS. This flaw in the design of these trials has been extensively pointed out

---

[a] Increased height reduction on radiologic images at follow-up (≥ 20% in comparison to initial imaging)
[b] ≥ 15% kyphosis and/or ≥ 10% scoliosis and/or ≥ 10% dorsal wall height reduction and/or vertebral body height loss ≥ 20%
[c] the RAND study panel included 4/12 UK experts

(cf. section 5.3 Medtronic submissions) but is not reflected in the report. The individual-patient level meta-analysis conducted on the aforementioned studies[8] reported that 24 participants were required in each treatment group to show a 2.5 unit reduction in pain score[d]; however, only 25 of 106 PVP patients in the meta-analysis had onset of pain before 6 weeks – i.e. Acute fractures. Furthermore, it is unknown if all these patients had severe pain at baseline, or if they were a mix of patients with mild, moderate or severe pain. Equally important, fracture severity was not reported in the INVEST study[6] and only 23% of fractures in Buchbinder's study[7] were reported as "severe", albeit the staging of fracture severity is not provided so not comparable to other studies.

Hence the clinical review in the report is potentially misleading by including these studies. This is particularly the case given that the AG considered these studies to be the best quality trials available to evaluate vertebral augmentation. Furthermore, all parameters in the AG's model that are estimated using the results of these trials are unreliable. This is of significant importance given the predictive analysis of QALY improvement suggested that worse health states at baseline provide larger gains in QALY (Borgström 2012, Medtronic submission Supplementary document 8).

In contrast, the model submitted by Medtronic focuses on the relevant patient population by using FREE (>50% of patients had more than 25% of deformity) and VERTOS II (>60% of patients had more than >40% deformity) and estimates parameters based on appropriate clinical evidence. The concern of placebo effect should be weighted not only against the bias of introducing these studies as source for utility gain but also against emerging evidence suggestive of reduced morbidity for VA patients and BKP in particular using more objective measures (Edidin 2012 Morbidity[e]); as well as the 1 year results of the early terminated RCT comparing BKP to PVP (KAVIAR,

[d] assuming a SD of 3.0, significance level of 5% and 80% power
[e] Supplementary references to this response

NCT00323609[f]) that observes a trend of a lower rate of subsequent fractures in favour of BKP.

3. Not scoped and inappropriate inclusion of comparator – Operative Placebo Local Anaesthesia (OPLA)

The failure to characterise the correct patient population for vertebral augmentation has also led to the inclusion of an inappropriate comparator– (OPLA) - into the report and model with the suggestion that this sham-procedure has the potential to be a second line treatment alternative for OVCFs.

OPLA would not be considered appropriate for the vertebral augmentation population clarified in point 1 above. Patients who are most likely to benefit from OPLA are those who develop facet joint pain after the natural healing of their fracture and may experience short term alleviation of their pain due to the injection; albeit the long term impact is less clear and will not address their post-fracture segmental kyphosis

4. Underestimation of the relative benefit of BKP

A further limitation of the AG report is that the relative benefit of BKP compared to both OPM and PVP is likely to be underestimated and imprecise in the majority of scenarios modelled. The problem is manifested as follows:

Firstly, utilities used for economic modelling were either derived from regression analysis of the VAS pain scale against the EQ-5D ('mapping') or by using pooled EQ-5D scores at 4 weeks from INVEST[6], Buchbinder[7] and FREE[9] studies directly . Mapping utilities from VAS pain may ignore between 40 to 55% of the balloon kyphoplasty effect which relate to economically relevant dimensions of HRQoL - mobility and self-care. This suggestion derives firstly, from dimensional analysis undertaken on patient-reported outcomes instruments from FREE[9] and BKP data from SwissSpine Registry

[f] http://www.clinicaltrials.gov/ct2/show/results/NCT00323609?term=Kaviar&rank=1

revealing the relative contribution of each dimension to the overall EQ-5D value (Borgström 2012, Medtronic submission Supplementary document 8; Borgström SSR analysis 2012[e]). Secondly, from available exploratory factorial analysis conducted on EQ-5D and ICECAP-O[10] as well as EQ-5D and OHS[11] suggestive that the scales are more complements than substitutes. As indicated by the AG, *mapping has the advantage of incorporating data from all studies and thus will not discard data, although will not be as precise as using EQ-5D directly from the trials*. This imprecision is probably relevant, as by removing the INVEST study from the mapping the fit of VAS pain to EQ-5D increases from an r^2 of 0.62 to 0.86.

The second problem is that the use of a network meta-analysis included studies with meaningful differences between randomised groups in VAS pain scores at baseline. By conducting the meta-analysis in terms of absolute VAS rather than difference from baseline, the results may well be biased. Furthermore, as the FREE study[9] showed the smallest difference between groups at baseline (likely due to a larger sample size, n = 300), the discrepancies in the PVP vs. OPM baseline values may have biased against the BKP vs. PVP comparison. This would impact on the results of the network meta-analysis and the scenarios in which these are used in the cost-effectiveness analysis. We would, therefore, suggest that the scenarios using the results of the meta analysis and VAS mapping (scenarios 1, 3, 5) should not be considered in the Appraisal Committee's deliberations.

The third problem relates to the choice of EQ-5D data for scenarios 2, 4 and 6.The AG have selected individual trials for each sensitivity analysis, forcing them to assume equivalence of BKP and PVP and thus resulting in BKP being dominated in the cost-effectiveness analysis scenarios in which the mortality benefit of BKP over PVP is removed (scenarios 4 and 6). To adequately capture the full utility impact of the differences observed on segmental spinal deformity correction between BKP and PVP, a more sensitive instrument on this dimension is likely needed. For example, the recent analysis on radiographic measurements and relationship with other outcomes from the FREE study observed a significant association of improved physical

functioning (SF-36 PCS) with increased correction of segmental kyphosis (Van Meirhaeghe 2012[e]). Furthermore, the correlation analysis of QALY/AUC_{score} improvement in FREE has shown VAS-pain and RMDQ give modest explanations for the variance in EQ-5D (12% and 15%) and SF-36 utility (18% and 27%). This suggests that these measurements are not appropriate predictors for overall quality of life, at least in comparison with multi-dimensional instruments such as EQ-5D and SF-36 (Borgström 2012, Medtronic submission Supplementary document 8).

The fourth problem relates to how the relative benefit of BKP is modelled with respect to the mortality effect. Although the mortality effect of vertebral augmentation interventions is considered plausible by the AG, mainly due to the strength of effect, no consideration is given to its plausibility and consistency. The most plausible assumption is that BKP shows a difference in size of effect on mortality, relative to PVP, as Medicare data analysis (Edidin 2012, Medtronic submission Supplementary document 3) adopted thorough propensity score analysis to reduce selection bias, used a large sample size (858,978 patients) and its findings were partially replicated in a smaller European healthcare setting (AOK Niedersachsen German sickness fund, 2.4 million insurants in 2011, 3'607 included in survival analysis) (Lange 2012, Medtronic submission Supplementary document 4). Furthermore, given the well-known cascade from a primary vertebral fracture to hyperkyphosis to increased morbidity and mortality, the mortality benefit is most likely to be linked to a meaningful impact on physical functioning subsequent to spinal deformity correction, particularly for this co-morbid patient population.

More specifically, the differences in morbidity risks from Medicare (Edidin 2012 Morbidity[e]) that has emerged since Medtronic submission reports that BKP vs. PVP propensity-matched OVCF patients that survived first year had -16% risk of being admitted to hospital with pneumonia; -22% risk of death with pneumonia; -4% risk of subsequent hospitalisation and -6% risk of Urinary Tract Infections (UTI). Additionally, it is observed that same matched cohorts of BKP vs. OPM (but not PVP) patients had -12% risk of myocardial

infarctions/ cardiac complications and -12% risk of being admitted with Deep Vein Thrombosis (Edidin et al 2012).

5. Inaccurate acquisition cost of balloon kyphoplasty

The acquisition cost modelled by the AG is the list price cited for BKP (£2663) in the Medtronic submission which is significantly higher than the average selling price (ASP £1900) as sourced from NHS tender offerings. This tender process is transparent and consistent, with the price offering agreed for a given timeframe in line with tender specifications.

Further to an unsolicited request from NICE c/o Stuart Wood (Technology Appraisal Team), we revised our submission to formally release the ASP for BKP from commercial in confidence (CIC) and, under sections 1.11 ,6.5.8, 8.5.4 (table), 8.5.5 (table) and 8.5.9 (table), publically disclosed an ASP of £1900. We also amended our check list to align with this revised submission (26/07/12).

Therefore, Medtronic suggest that AG either use our ASP in the foundation scenario or run sensitivity analysis on ICER estimates.

Medtronic
Alleviating Pain · Restoring Health · Extending Life

References

1. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet*. 2009;373(9668):1016–24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19246088. Accessed June 6, 2011.

2. Klazen CAH. Percutaneous Vertebroplasty and Pulmonary Cement Embolism : Results from VERTOS II. *Ajnr. American Journal Of Neuroradiology*. 2010:60–62.

3. Grohs JG, Matzner M, Trieb K, Krepler P. Minimal invasive stabilization of osteoporotic vertebral fractures: a prospective nonrandomized comparison of vertebroplasty and balloon kyphoplasty. *Journal of spinal disorders & techniques*. 2005;18(3):238–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15905767. Accessed September 13, 2012.

4. Movrin I, Vengust R, Komadina R. Adjacent vertebral fractures after percutaneous vertebral augmentation of osteoporotic vertebral compression fracture: a comparison of balloon kyphoplasty and vertebroplasty. *Archives of orthopaedic and trauma surgery*. 2010;130(9):1157–66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20449750. Accessed September 13, 2012.

5. Röllinghoff M, Siewe J, Zarghooni K, et al. Effectiveness, security and height restoration on fresh compression fractures--a comparative prospective study of vertebroplasty and kyphoplasty. *Minimally invasive neurosurgery : MIN*. 2009;52(5-6):233–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20077364. Accessed September 13, 2012.

6. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *The New England journal of medicine*. 2009;361(6):569–79. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2930487&tool=pmcentrez&rendertype=abstract. Accessed May 30, 2012.

7. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *The New England journal of medicine*. 2009;361(6):557–68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19657121. Accessed June 6, 2011.

8. Staples MP, Kallmes DF, Comstock B a., et al. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ*. 2011;343(jul12 1):d3952–d3952.

Available at: http://www.bmj.com/cgi/doi/10.1136/bmj.d3952. Accessed July 20, 2011.

9. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21337428. Accessed June 18, 2011.

10. Davis JC, Liu-Ambrose T, Richardson CG, Bryan S. A comparison of the ICECAP-O with EQ-5D in a falls prevention clinical setting: are they complements or substitutes? *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22723152. Accessed August 31, 2012.

11. Oppe M, Devlin N, Black N. Comparison of the underlying constructs of the EQ-5D and Oxford Hip Score: implications for mapping. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 14(6):884–91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21914510. Accessed September 13, 2012.