The clinical and cost effectiveness of biventricular pacing for patients with severe heart failure.

Addendum Report – January 2005 [Updated January 2006]

A West Midlands Health Technology Assessment Collaboration Report

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONFLICTS OF INTEREST: NONE

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Thanks to Dr Russell Davies, Consultant Cardiologist, Heartlands Hospital, Birmingham and Mr Paco Leyva, Cardiac Surgeon, Good Hope Hospital, Birmingham for their comments on previous drafts of this report and local implant data and costs.

West Midlands Regional Evaluation Panel

Recommendation

BVP alone (CRT-P) is recommended based on Level I evidence for selected heart failure patients (New York Heart Association class III or IV, QRS interval> 120 msec and LVEF<=35%, sinus rhythm)

Although randomised controlled trials have been undertaken on BVP many of these have not been undertaken from the UK context. Equipment and cost differences between these trials and UK practice limit the generalisability of the findings. The panel therefore made the above recommendations on the evidence from, or generalisable to, the UK context.

The National Institute for Health and Clinical Excellence is expected to provide guidance on the use of BVP to the NHS in England and Wales in mid-2007. This guidance will supersede the above recommendation.

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Anticipated expiry date

Mid 2007

Executive Summary

Biventricular pacing (or 'cardiac resynchronisation therapy') is increasingly being used as an intervention for heart failure patients with persistent symptoms who are refractory to optimal medical therapy. Cardiac resynchronisation includes biventricular pacing and implantable cardioverter defibrillators. Given the specific nature of the original West Midlands referral, this report focuses on biventricular pacing alone.

An updated meta-analysis of 8 randomised controlled trials (across 2,390 patients) showed that the addition of biventricular pacing to optimal medical care, in selected heart failure patients (NYHA class II and III heart failure patients with an ejection fraction of $\leq$ 0.35, QRS duration $\geq$120msec and who were still symptomatic despite optimal drug therapy), significantly reduces both all-cause mortality (pooled relative risk: 0.76, 95% CI: 0.65 to 0.90, fixed effects) and heart failure rehospitalisation (pooled relative risk: 0.51, 95% CI: 0.40 to 0.63 fixed effects) and improves quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire (Mean difference: -8.73, 95% CI: -12.00 to –5.46 random effects).

Four published economic evaluations have assessed the cost effectiveness of biventricular paving. The wide range in incremental cost per quality adjusted life year (QALY) of biventricular pacing reported by these studies (£12,368/QALY to £72,765/QALY at 2005 UK prices) reflects the variety of assumptions and modelling approaches applied. The incremental cost per QALY was highly sensitive to the assumed impact of biventricular pacing on quality of life and the level complications and device and other healthcare costs. The CARE-HF trial indicates that biventricular pacing seems to be cost effective (mean €43,596 per QALY/£229,982 /QALY) from the perspective of the UK NHS.

NICE are due to issue their guidance to the NHS in England and Wales on the use of cardiac resynchronisation therapy in heart failure in March 2007.

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1. Background

Biventricular pacing (BVP) or 'cardiac resynchronisation therapy' is increasingly being used as an intervention for patients with severe heart failure persistent symptoms that are refractory to conventional drug therapy. BVP was referred in late 2002 to the West Midlands Health Technology Assessment Collaboration (WMHTAC) for evaluation and subsequent guidance from the West Midlands Regional Evaluation Panel (REP).

Cardiac resynchronisation includes biventricular pacing and implantable cardiovertor defibrillators. However, given the specific nature of the regional referral, this report focuses on biventricular pacing alone.

In August 2003, Sarah Hancock and Josie Sandercock of WMHTAC completed their assessment report '*The clinical and cost effectiveness of biventricular pacing for patients with severe heart failure with left ventricular dysfunction'*. This report comprised a systematic review and meta-analysis of the clinical trial literature on BVP and an outline cost effectiveness model.

Ms.Sandercock presented a preview of this report to the West Midlands REP meeting on 10th June 2004. Following discussion by the Panel, it was agreed that two further key pieces of work should be undertaken before the Panel could issue its recommendation on this topic:

(1) Update of the clinical effectiveness literature – At the time of writing, of the Hancock and Sandercock report it was known that a large randomised controlled trial (RCT) was about to be published – the COMPANION trial. It was agreed that the systematic review and meta-analyses be updated on the basis of this new trial evidence. Since then a large European RCT has also been published (CARE-HF).

(2) Assessment of cost effectiveness – Given the inadequacy of the clinical evidence at that time, no cost effectiveness analysis was undertaken by Hancock and Sandercock. No economic analyses at that time were published. However, an estimate of cost effectiveness of BVP was required for the REP committee.

This addendum report aims to address these two requests for additional data.

2. Format and aim of this report

The original intention of this report was to update the Hancock and Sandercock systematic review and then use these findings to populate their economic model in order to explore the cost effectiveness of BVP. However, in the process of updating the literature search for the purposes of the report, a number of key publications were identified. McAllister *et al* published a systematic review of the BVP clinical trial literature in late 2004 [1,3]. In April 2005 the results of a large European randomised controlled trial (CARE-HF) were published [2]. Finally, four cost effectiveness analyses of the use of BVP in heart failure have been published over the last 12-months [4-7].

The aim of this report is to provide a concise summary of this evidence base. The report is organised into three sections:

- a summary of the clinical effectiveness of BVP
- a summary of the cost effectiveness of BVP
- a discussion of the implications of these findings to the West Midlands.

Details of the epidemiology of heart failure, current treatment options for heart failure, plus a description of BVP and its mechanism of action, can be found in the report of Hancock and Sandercock.

3. Clinical effectiveness of BVP

3.1 Quality of the evidence base

The systematic review and meta-analysis of McAlister *et al* (2004) was appraised using the Oxford CASP Programme checklist (see Table 1). The review was judged to be of good quality i.e. comprehensive literature searching (where relevant, the authors' unpublished data was sourced from trialists), independent study selection and data extraction, and consideration of a range of efficacy and safety outcomes.

Although the paper did not report the quality of the included trials, details of the trial quality are provided in the full report by the authors on the US Agency for Healthcare and Quality (ARHQ) website [2]. The quality of included trials ranged from 'moderate' to 'good' (Jadad score $\geq$ 3 out of a possible maximum

of 5). It is worth noting, the authors' comments in the discussion section, that the main methodological issue of the included trials was not their internal validity but external validity - patients were randomised following a run in test period to confirm that they were suitable for BVP. This would tend to inflate the estimates effectiveness of BVP of these trials relative to 'real' clinical practice. The recent CARE-HF trial was judged to be of moderate quality (Jadad score; 3 out of 5) – the trial report provided no details of randomisation concealment procedure and was not blinded. The characteristics of the three major RCTs (MIRACLE, COMPANION and CARE-HF) are summarised in Table 2.

3.2 Characteristics of recruited patients

All trials enrolled exclusively NYHA class II and III heart failure patients with an ejection fraction of ≤ 0.35 and evidence electomechanical dyschromy (i.e. QRS duration $\geq$120msec) and who were still symptomatic despite optimal drug therapy (ACE or ARB and beta-blockers). The CARE-HF recruited a further 813 patients based on the same inclusion criteria with the addition of a left ventricular end-diastolic volume of at least 30mm (indexed to height).

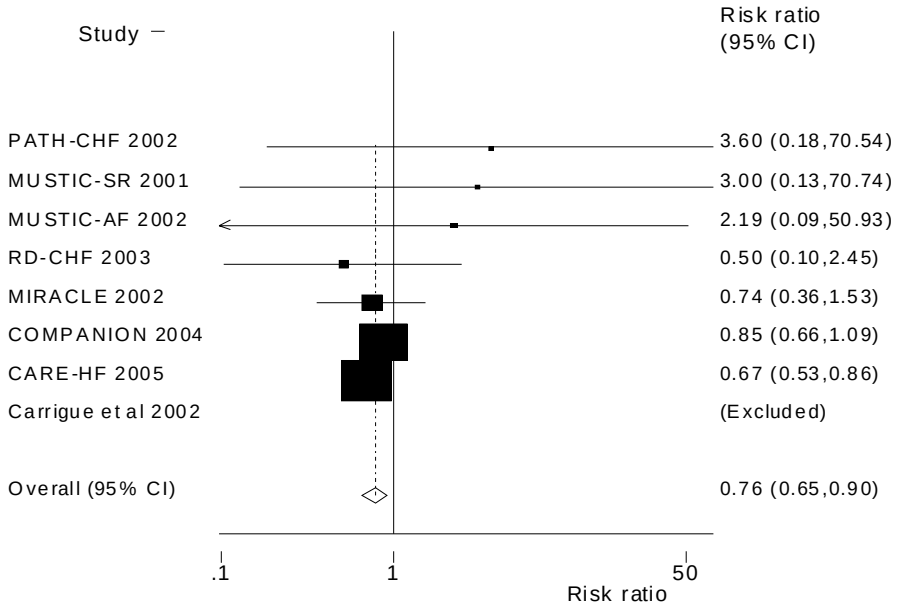
3.3 Scope of included RCTs

The reported meta-analyses included both trials that compared BVP implantation alone (PATH-CHF, 2002; MUSTIC-AF, 2002; MUSTIC-SR, 2001; MIRACLE, 2002; COMPANION, 2004 and CARE-HF, 2005) and BVP combined with an implantable cardioverter-defibrillator (ICD) (CONTAK-CD, 2003; MIRACLE-ICD, 2003 & COMPANION-CD, 2004) to medical therapy. The authors showed through meta-regression that there was no statistically significant difference in outcome of BVP either with or without an ICD.

3.4 Findings

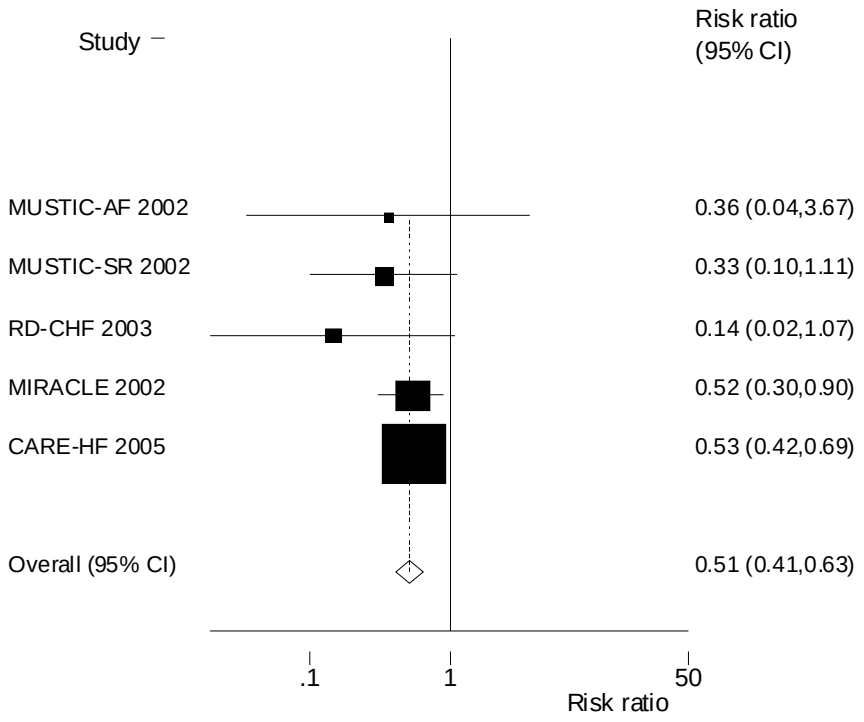
Given the West Midlands request that initiated this report was specifically related to BVP, a reanalysis of the McAllister (2004) review was undertaken pooling only RCTs that excluded patients with ICDs or combined BVP and ICD devices. Data was available for the reanalysis of all-cause mortality, rehospitalisation due to heart failure and health-related quality of life (see

Figures 1 to 3). Fixed effect meta-analysis was used, except where there was evidence of statistically significant heterogeneity.



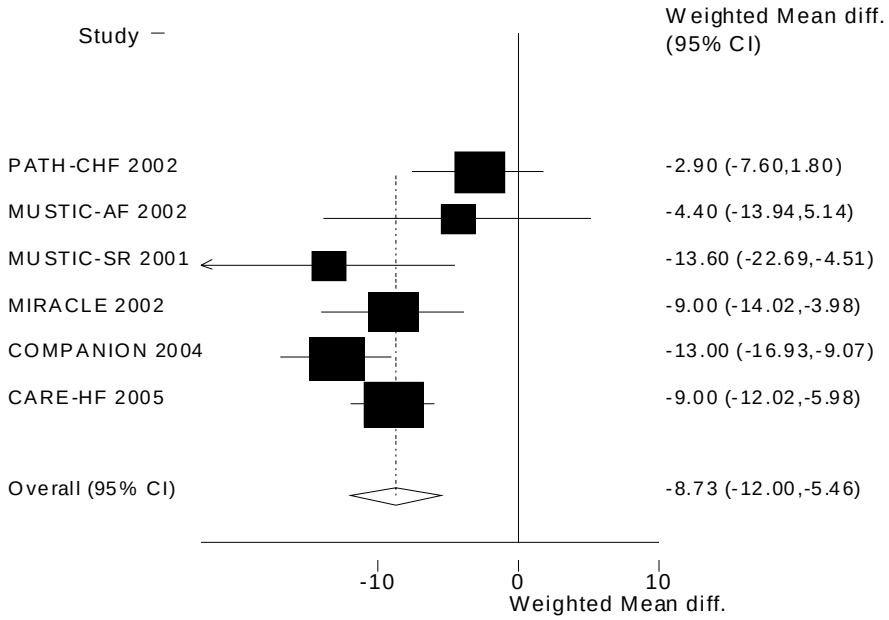
Heterogeneity chi-squared = 4.17 (d.f. = 6) p = 0.654 [fixed effects model]

Figure 1. All-cause mortality with BVP (no ICD device) versus controls.



Heterogeneity chi-squared = 2.27 (d.f.= 4) p = 0.687 [fixed effects model]

Figure 2. Heart failure rehospitalisation with BVP (no ICD device) versus controls.



Heterogeneity chi-squared = 12.32 (d.f.= 4) p = 0.015 [random effects model]

Figure 3. Change in quality of life with BVP (no ICD device versus control (based on Minnesota Living with Heart Failure Questionnaire).

In summary, these updated meta-analyses demonstrate that, in selected heart failure patients, when compared to optimal medical therapy alone, BVP significantly reduces all-cause mortality and the risk of rehospitalisation due to heart failure and improves patient's health related quality of life.

Based on both RCT and observational cohort reports, the McAlister (2004) review reported a device failure rate of 10% (95% CI: 9 to 11%) across 17 studies in 3673 patients. Some 7%, 9%, 1.4% and 2% experienced device malfunction, lead dislodgement, infection and new arrhythmias respectively in the 6-months post-implant follow up.

4. Cost Effectiveness of BVP

4.1 Quality & scope of evidence base

Four published economic evaluations were identified that address the question of cost effectiveness of the addition of BVP to optimal medical care, and all reported their results as incremental cost per quality adjusted life year (QALY) (see Table 3) [4-7]. Three of these studies were effectively economic analyses of the major RCTs (MIRACLE, CARE-HF and COMPANION) while the fourth was based on a Markov model using effectiveness data sourced

from a meta-analysis of all RCTs (CARE-HF omitted as not published at that time). All studies appeared to fulfil the majority of the quality criteria of the checklist of Drummond and Jefferson for economic evaluations [8]. The principle limitation was the lack of reported sensitivity analyses.

4.2 Findings

The incremental cost effectiveness of BVP across studies ranged from US$ 19,600 (£12,368) per QALY in the analysis of Kuntz to $107,800 (£72,765) per QALY reported by Nichol *et al*. This wide range in incremental cost per QALY reflects the variety of assumptions and modelling approaches applied across studies. Nevertheless, three of the four studies reported a mean cost per QALY below the threshold £30,000 per QALY.

The principle reason for the higher incremental cost per QALY was the substantially higher device costs used in the US-based analysis of Nichol *et al*. However, there was also considerable variation in the absolute mean QALY values (for both BVP and medical care) and mean incremental difference (0.26 to 0.47) between the two, although varying time horizons would partially explain these differences.

The CARE-HF analysis was conducted by Calvert *et al* from the perspective of UK NHS and is therefore probably the most relevant to the West Midlands. The mean cost per QALY reported by this study was Euros 43,596 (£29,982) per QALY. At a threshold of £20,000 per QALY the authors of this study reported a probability of 83% that BVP was cost effective compared to optimal care.

5. Service delivery implications for the West Midlands

The National Institute for Clinical Excellence (NICE) Guidelines for Chronic Heart Failure published July 2003, state that *cardiac resynchronisation therapy (i.e. BVP with or without an ICD) should be considered in selected patients with left ventricular systolic dysfunction (left ventricular ejection fraction ≥35%), drug refractory symptoms, and QRS duration > 120 msec* [9].

Early studies suggested that 25% or more of new heart failure patients would be eligible for BVP (i.e. class III or IV with a major conduction disorder and

refractory to medical therapy) [5,6]. However, recent unpublished utilisation data from Canada (Edmonton) suggests that only 1-2% of new heart failure patients (i.e. ~20% of those referred to heart failure clinics) are actually receiving BVP (McAllister, personal communication, 2005).

Currently, four centres (City, Dudley, Good Hope and Queen Elizabeth) in the West Midlands provide a BVP implantation service. It is estimated that about 7.1% of all referrals to the Sandwell heart failure service between July 2003 and November 2003 required BVP, equivalent to an incidence of between 90 to 100 new cases per million population (based on presentation by Anna Kydd, 2004). The local cost of a BVP procedure (including equipment, staff, hospital stay and 12-month follow up) is about £7,500 per patient (Dr Leyva, Personal communication, 2005).

6. Conclusions

BVP (without combination with an ICD) appears to be a clinically effective adjunct to optimal medical treatment in selected heart failure patients. However, its cost effectiveness remains less certain although a recent analysis (based on the CARE-HF trial) indicates that BVP seems to be cost effective from a UK NHS perspective.

The cost effective implementation of BVP within the West Midlands is likely to depend on cost of the BVP procedure (device and staffing) to the local health economy as well as the careful application of criteria for selection of suitable patients. Further research is needed to assess the place of BVP combined with ICD in the management of heart failure, and to identify those patients where BVP is likely to most cost effective.

NICE is due to issue guidance to NHS in England and Wales on cardiac resynchronisation therapy in severe heart failure in March 2007 [10].

Table 1. Critical Appraisal of Systematic Review of McAllister et al [1]

THE UNIVERSITY
OF BIRMINGHAM

West Midlands Health Technology Assessment Collaboration (WMHTAC):

McAlister FA et al. Systematic review: cardiac resynchronisation with symptomatic heart failure

***Ann Intern Med* 2004;381-90**

10 questions to help you make sense of a review

General comments

- Three broad issues need to be considered when appraising a systematic review:

A/ Are the results of the review valid?

B/ What are the results?

C/ Will the results help locally?

- The 10 questions on the following pages are designed to help you think about these issues systematically.
- The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.
- There is a fair degree of overlap between several of the questions.
- You are asked to record a "yes", "no" or "can't tell" to most of the questions.
- A number of italicised prompts are given after each question. These are designed to remind you why the question is important. There will not be time in the small groups to answer them all in detail!

The 10 questions are adapted from Oxman A.D. et al Users' Guides to The Medical Literature, VI How to us an overview, JAMA 1994; 272 (17): 1367-1371.

These materials were developed by the CASP* team in Oxford.

*CASP (Critical Appraisal Skills Programme) helps health service decision-makers develop skills in appraising evidence about clinical effectiveness. It works with local programmes for evidence-based health care.

.A/ Are the results of the review valid?

Screening Questions

1. Did the review address a clearly focused question? HINT: An issue can be 'focused' in terms of • *the population studied* • *the intervention given* • *the outcome considered*	**Yes** **Can't tell** **No** ☐√ ☐ ☐ **This paper assessed the efficacy and safety of BVP (±ICD) in patients with symptomatic (level III or IV) HF**
2. Did the authors look for the appropriate sort of papers? *HINT: The 'best sort of studies' would* - *address the review's question* - *have an appropriate study design (usually RCTs for papers evaluating interventions)*	**Yes** **Can't tell** **No** ☐√ ☐ ☐ **For efficacy – RCTs only** **For safety – RCTs plus prospective cohort study**

Detailed questions

3. Do you think the important, relevant studies were included? *HINT Look for* - *which bibliographic databases were used* - *follow up from reference lists* - *personal contact with experts*	**Yes** **Can't tell** **No** ☐√ ☐ ☐ **Detailed search of electronic bibliographies undertaken Importantly included data on FDA website which is otherwise not available. Searched up to May 2004.**

- *search for unpublished as well as published studies* - *search for non-English language studies*	
4. Did the review's authors do enough to assess the quality of the included studies? HINT The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies' results ("All that glisters is not gold" Merchant of Venice – Act II Scene?)	**Yes** **Can't tell** **No** ☐ ☐ ☐√ **No assessment of quality undertaken. However, the included RCTs appeared to be of good quality. Furthermore, the authors comment in the discussion section that main methodological issue was not internal validity but external validity as patients randomised following a run in test period to confirm that they were suitable for BVP. This would tend to inflate the effectiveness of BVP relative to 'real' clinical practice.**
5. If the results of the review have been combined, was it reasonable to do so? *HINT: Consider whether* - *the results were similar from study to study* - *the results of all the included studies are clearly displayed* - *the results of the different studies are similar* - *the reasons for any variations in results are discussed*	**Yes** **Can't tell** **No** ☐√ ☐ ☐ **Authors meta-analysed data used both fixed and random effects meta-analysis according to level of outcome heterogeneity. Furthermore they explored this heterogeneity using meta-regression.**

B/ What are the results?

6. What are the overall result of the reviews? *HINT: Consider* - if you are clear about the review's 'bottom line' results: - what these are (numerically if appropriate) - how were the results expressed (NNT, odds ratio etc.)	**<u>Efficacy</u>** **All cause morality: RR 0.79 (95%CI: 0.66 to 0.96)** **Cardiac mortality: RR 0.60 (95%CI: 0.36 to 1.01)** **HF rehospitalisations: RR 0.90 (95%CI: 0.41 to 1.12)** **Quality of life: Minnesota living with HF questionnaire – mean improvement 7.6 pts (95%CI: 3.8 to 11.5)** **<u>Safety</u>** **Peri-implantation risk: death 0.4% (95%CI: 0.2 to 0.7%)** **Postimplantation risk: malfunctioning 7% (95%CI: 5 to 8%)** **Device failure: 10% (95%CI: not reported)**
7. How precise are the results? HINT: Look at the confidence intervals, if given	**See above**

C/ Will the results help locally?

8. Can the results be applied to the local population? *HINT: Consider whether* - *the patients covered by the review could be sufficiently different to your population to cause concern* - *your local setting is likely to differ much from that of the review*	**Yes** ☐ **Can't tell** ☐ **No** ☐ **Data not available to assess if recruited patients within trials are reflective of patients implanted in West Midlands**
9. Were all important outcomes considered?	**Yes** ☐√ **Can't tell** ☐ **No** ☐ **Included clinical outcomes both in terms of benefits and harms plus quality of life**
10. Are the benefits worth the harms and costs? *Even if this is not addressed by the review, what do you think?*	**This paper comes to a generally positive conclusion on BVP** **i.e. in selected patients, BVP was associated with significant reduction in mortality (partic. mortality from progressive) and clinical meaningful improvement in quality of life with small increase risk of serious AEs** **Cost effectiveness is dealt with the accompanying modelling paper by Nichol et al (2004).**

Table 2. Characteristics of three major RCTs

	N*	Country	Patient characteristics	Primary outcomes	Follow up	Jadad score
MIRACLE	453	US & Canada	Mean age: 64 (SD 11) % male: 68% NYHA Class III: 90% Mean QRS interval: 166 (SD 21) Mean LVEF: 22% (6)	NYHA class, quality of life, 6-minute walk test	6-months	5
COMPANION	925	US	Mean age: 66 % male: 68% NYHA Class III: 85% Mean QRS interval: 158 Mean LVEF: 22	All-cause mortality & hospitalisation	12-months	3
CARE-HF	813	Europe	Median age: 67 % male: 73% NYHA Class III: 75% Mean QRS interval: 160 Median LVEF: 25%	Time to death from or hospitalization for any cause.	12-months	3

***Excludes patients with combined BVP and ICD.**

Table 3. Characteristics of four economic evaluations

	Nichol, 2004 [3]	Kunz, 2005 [4]	Calvert, 2005 [5]	Feldman, 2005 [6]
Stated policy question	BVP vs. medical care	BVP vs. medical care	BVP vs. medical care	BVP vs. medical care
Method of economic analysis	Markov model	Decision tree model	Trial-based	Trial-based
Perspective	Healthcare	Healthcare	Healthcare	Healthcare
Time horizon	Lifetime	1-years	10-years	7-years
Source of effectiveness data	Meta-analysis of RCTs (except CARE-HF)	Single RCT [MIRACLE]	Single RCT [CARE-HF]	Single RCT [COMPANION]
Source of costs	Literature, manufacturer list prices	Routine data, expert opinion, manufacturer list prices	Within trial resources & costs, manufacturer list prices	Within trial resources & costs
Source of utilities	Time trade off population study	Published values	EQ-5D values of patients in trial	Published values
Cost of device [local currency & UK £s*]	US$ 33,495 (+ICD) £22,609	€7,500 £5,319	€5,805 & €19,977 (+ICD) £3,992 & £13,754	US$ 7,849 & $20,461 (+ ICD) £4,592 & £12,910
Currency & year of costs	US$ 2003	€ 2005	€ 2005	US$ 2004
Discounting	3% for benefits & costs	Not stated	3.5% for benefits & costs	3% for benefits & costs
Funder	Government	Industry	Industry	Not stated
Comments	Assumed no HRQoL benefit with BVP	Based on a German healthcare scenario	18-month RCT based survival extrapolated to 10-yrs	Costs based on DRG costs 2-yr RCT based survival extrapolated to 7-yrs

*Converted to £2005 using purchasing parity power and (where appropriate) inflation rates; +includes implantation cos

Table 4. Results of economic evaluations [local currency & UK £s*

Author, year	BVP QALY	Medical therapy QALY	BVP total cost	Medical therapy total cost	Cost per QALY (95% CI or range)
7Nichol, 2004 [3]	2.92	2.64	US$ 64,6400	US$ 34,400	$US 107,800 ($79,800 to $155,500) £72,765 (£53,865 to £104,962)
Kunz, 2005 [4]	0.70	0.54	€10,090	€4,210	€36,600 (€22,400 to €36,600) £29,257 (£15,886 to £25,957)
Calvert, 2005 [5]	1.42	1.19	€15,795	€20,100	€43,596 (-€146,236 to €223,849) £29,982 (-£100,572 to £153,949)
Feldman, 2005 [6] **BVP** **BVP+ICD**	4.19 4.51	3.64 3.64	US$ 59,870 US$ 82,236	US$ 46,021 US$ 46,201	US$ 19,600 (-$331,700 to $399,100) £12,368 (-£209,302 to £144,075) US$ 43,000 (-$90,300 to $201,000) £27,130 (-£56,579 to £126,831)

*Converted to £2005 using purchasing parity power and (where appropriate) inflation rates

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