

# The cost-effectiveness of real-time pulmonary artery pressure monitoring in heart failure patients: a European perspective

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## Aims

Heart failure (HF) treatment guided by physicians with access to real-time pressure measurement from a wireless implantable pulmonary artery pressure (PAP) sensor (CardioMEMS), has previously been shown to reduce HF-related hospital admissions in the CHAMPION trial. However, uncertainty remains regarding the value of CardioMEMS in European health systems where healthcare costs are significantly lower than in the USA.

## Methods and results

A Markov model was developed to estimate the cost-effectiveness of PAP-guided treatment of HF using the CardioMEMS™ HF system compared with usual care. Cost-effectiveness was measured as the incremental cost per quality-adjusted life year (QALY) gained. In the base case analysis over a time horizon of 10 years, PAP-guided HF therapy increased cost compared with usual care by £10 916 (€14 030). QALYs per patient for usual care and PAP-guided patients were 2.57 and 3.14, respectively, reflecting an increase of 0.57 QALYs with PAP-guided treatment. The resultant incremental cost-effectiveness ratio (ICER) is £19 274 (€24 772) per QALY gained. The base case analysis did not include staff time, due to a lack of data concerning this variable. Running the model with estimated staff time included resulted in an increased ICER of between £22 342 and £25 464 per QALY gained (€28 709–32 721).

## Conclusion

The analysis indicates that integrating wireless PAP monitoring into the management of UK HF patients is likely to be a cost-effective addition to the HF treatment pathway for appropriate patients.

## Keywords

Heart failure • Pulmonary artery pressure monitoring • Telemonitoring • Cost-effectiveness

## Introduction

In Europe, between 1% and 2% of the population have heart failure (HF).<sup>1</sup> The syndrome is associated with reduced life expectancy<sup>2</sup> and an impaired quality of life.<sup>3</sup> In the UK, there were 160 000 hospitalizations for HF in 2013/14,<sup>4</sup> with an in-hospital mortality of 9.5% and a 1-year mortality risk of 27%.<sup>5</sup> One estimate from England's National Institute for Health and Care Excellence (NICE) suggests that the National Health Service (NHS) spends £2.3 billion on HF (~2% of its total budget), with 70% of this expenditure due to hospitalization.<sup>6,7</sup> The situation is similar

in many European countries.<sup>8</sup> The primary symptom leading to hospitalization for worsening HF is dyspnoea, related to fluid retention and/or fluid redistribution, both of which are associated with an increase in pulmonary artery (PA) pressures (PAPs).<sup>9–12</sup>

A novel implantable haemodynamic sensor (CardioMEMS™ HF system, St. Jude Medical Inc., Atlanta, GA, USA) has been developed to provide physicians with remote real-time pressure measurements from the pulmonary artery. In a randomized controlled trial (RCT) of 550 NYHA class III HF patients with a previous HF hospitalization enrolled at 64 US hospitals, doctors that used these

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pressure measurements to guide their patients' medical therapy (treatment group) achieved a 33% reduction in HF-related hospitalizations over an average study duration of 15 months<sup>13</sup> compared with the control arm who had the device implanted but where the data were not used to guide management. The CardioMEMS sensor has been approved for use in the USA by the Food and Drug Administration (FDA), and in June 2016 the Heart Failure Association of the European Society of Cardiology (ESC) included the system in the ESC guidelines for the diagnosis and treatment of acute and chronic HF, indicating that the device may be considered for monitoring symptomatic patients with a previous HF hospitalization in order to reduce the risk of recurrent hospitalization (class IIb recommendation, level of evidence B).<sup>14</sup> Unlike other implantable devices, the CardioMEMS pressure sensor does not require a battery so can therefore, in theory, continue to function indefinitely.

Modelling can be used to estimate the cost-effectiveness of CardioMEMS by comparing its outcomes and costs with those of usual care. If these outcomes are estimated as quality-adjusted life years (QALYs), then the incremental cost-effectiveness ratio (ICER), or cost per QALY gained, can be calculated as the difference in costs divided by the difference in QALYs. This can aid decision-makers in determining whether a new intervention is 'value for money' and should be funded or reimbursed. In England, NICE typically recommends in favour of funding interventions with an ICER < £20 000/QALY, but requires considerable clinical benefit to recommend funding interventions between £20 000 and £30 000/QALY, and typically recommends against funding interventions with an ICER > £30 000/QALY. The aim of this study is to estimate the likely incremental cost per QALY of CardioMEMS compared with usual care, from a European perspective, so as to determine if this technology is likely to be recommended according to typical NICE thresholds for cost-effectiveness.

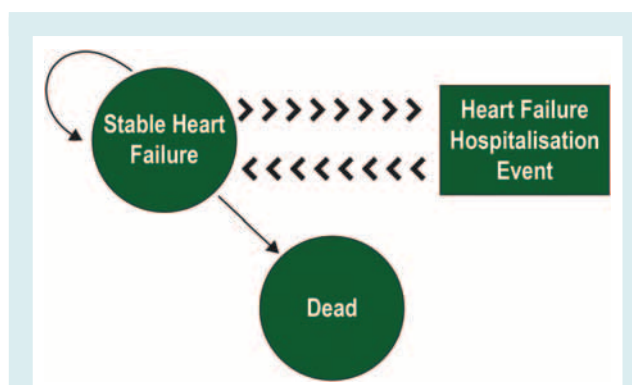
## Methods

### Scope of the model

A Markov model was developed in TreeAge 2015 (TreeAge Pro 2015, R1.0. TreeAge Software, Williamstown, MA, USA) to estimate the cost-effectiveness of PAP-guided treatment of HF using the CardioMEMS implantable pressure sensor compared with usual care strategies. The model was applied to a hypothetical population of 20 000 patients with HF.

The clinical effectiveness of PAP-guided treatment was derived from the pivotal RCT<sup>15</sup> on US patients which showed a significant decrease in hospitalizations related to HF, no effect on non-HF hospitalizations, and a trend towards mortality benefit. Costs estimated in the model included costs of the implantation procedure including the device and related complications, costs of HF-related hospitalizations, and costs of standard care.

Cost-effectiveness results were estimated as incremental cost per QALY gained, using mean values of 1000 probabilistic sensitivity analysis (PSA) runs, with each PSA run using different estimates for the risks, hazard ratios (HRs), costs, and utilities to capture the uncertainty in these input parameters. In effect, the computer simulation runs each of



**Figure 1** State transition diagram. The Markov model has two health states, stable heart failure (HF) and death. There is a monthly transition probability of moving from stable HF to dead state. Hospitalization is modelled as an event; there is a monthly risk of patients being hospitalized, which is used to estimate the costs/quality-adjusted life years. The patients are assumed to revert back to stable HF after hospitalization.

these 1000 sets of sampled values for each modelled patient (20 000); the base case results below are the mean values of these 20 million (20 000 × 1000) simulations.

### Model structure

The Markov model considered two health states: 'stable heart failure' and 'dead' (Figure 1). The patients were assigned a monthly probability of death based on their age and whether they had the intervention. Each month in the model, the patients who were alive were at risk of HF hospitalization or dying. HF hospitalization was not a health state but rather an event which patients might experience, an event which had costs associated with it. Patients who experienced HF hospitalization would then transition back to alive or dead at the end of that monthly cycle. Each patient then accrued QALYs and healthcare costs according to their hospitalization and treatment status. The model used a 10-year time horizon; the costs and QALYs were estimated using a healthcare payer perspective and discounted at an annual discount rate of 3.5%. It was assumed that patients entering the model were aged 70, the typical age of HF patients who are remotely monitored in the developed world.<sup>16</sup>

### Baseline mortality and hospitalization risk

The data for baseline risk of death were based on previous work by Griffiths *et al.* (in their 2014 model estimating cost-effectiveness of ivabradine for the treatment of HF).<sup>17</sup> They estimated mortality rates based on the CARE-HF trial, an RCT conducted on NYHA class III and IV HF patients with a prior hospitalization event and adjusted using UK interim life tables and increases with age in 5-yearly steps as shown in Table 1.

The baseline risk of hospitalization was based on a meta-analysis of 21 HF telemonitoring studies of 5715 patients, median age 70.7 (range 45–78 years), with 54% of patients in NYHA class III.<sup>16</sup> The average number of monthly HF-related hospitalizations for patients in usual care is shown in Table 1.

**Table 1** Summary of variables

Variable group	Variable description	Distribution used in PSA	Mean value	Source
Model settings	Age of patients entering the model		70	
	Model time horizon		10	
Costs	Cost of an implant complication	Fixed	£1090	UK reference costs
	Total cost of implant procedure including cost of equipment and device	Fixed	£12 000	Estimate
	Monthly cost to deliver medical care	fixed	£36	Griffiths <i>et al.</i> <sup>17</sup>
	Cost of a HF hospitalization	normal	£2038	UK reference costs
	Hourly rate for Band 5 nurse	Not run in base case Sensitivity analysis only	£36	PSSRU <sup>21</sup>
Hazard ratio	Hazard ratio reduction in HF hospitalization treatment cohort	Log normal	0.67	Abraham <i>et al.</i> <sup>37</sup>
	Hazard ratio reduction in mortality treatment cohort	Log normal	0.8	Abraham <i>et al.</i> <sup>37</sup>
Risks	Risk of implant complication	Fixed	0.0272	CHAMPION trial data
	Monthly risk of HF hospitalization	Beta	0.035	Klersy <i>et al.</i> <sup>16</sup>
Age-related mortality risk	Mortality risk age 45–50	Beta	0.00125	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 50–55	Beta	0.00197	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 55–60	Beta	0.00296	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 60–65	Beta	0.0046	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 65–70	Beta	0.00698	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 70–75	Beta	0.01044	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 75–80	Beta	0.01566	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 80–85	Beta	0.02136	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 85–90	Beta	0.02301	Griffiths <i>et al.</i> <sup>17</sup>
	Mortality risk age 90+	Beta	0.01864	Griffiths <i>et al.</i> <sup>17</sup>
Utility values for CardioMEMS patients	Trial utility at 1 month for treatment group	Normal	0.688	CHAMPION trial data
	Trial utility at 3 months for treatment group	Normal	0.646	CHAMPION trial data
	Trial utility at 6 months for treatment group	Normal	0.617	CHAMPION trial data
	Trial utility at 12 months for treatment group	Normal	0.653	CHAMPION trial data
Utility values for usual care patients	Trial utility at 1 month for usual care	Normal	0.645	CHAMPION trial data
	Trial utility at 3 months for usual care	Normal	0.569	CHAMPION trial data
	Trial utility at 6 months for usual care	Normal	0.566	CHAMPION trial data
	Trial utility at 12 months for usual care	Normal	0.547	CHAMPION trial data
Utility value for stable HF patients	Utility for patients with chronic HF	Fixed	0.57	Matza <i>et al.</i> <sup>19</sup>
Disutility for hospitalization	Disutility for HF hospitalization after 5 years	Triangular	–0.1	Klersy <i>et al.</i> <sup>16</sup>

HF, heart failure; PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit.

## Treatment effect

Hazard ratios associated with mortality and HF hospitalizations for CardioMEMS were taken from the CHAMPION trial, and were applied to the baseline monthly risk of mortality and HF hospitalization described above. The HRs used in the model are presented in *Table 1*. Due to the uncertainty regarding the mortality effect at this time, it was decided not to model the mortality effect beyond 5 years, after which the mortality risk is assumed to be the same for both cohorts within the model.

Prior to entering the Markov model, a small proportion (2.7%) of patients in the CardioMEMS cohort were assumed to experience an implant-related complication, based on data from the CHAMPION trial.<sup>15</sup>

## Health-related quality of life

Health-related quality of life (or utilities) for the patients was based on the European Quality of Life (EuroQoL) Five Dimensions, three level questionnaire (EQ-5D-3L) data, collected from the patients within the CHAMPION trial at 1, 3, 6, and 12 months. Mean utility values calculated over time for both cohorts (i.e. CardioMEMS and usual care) are presented in *Table 1*.

After 12 months, utility values were assumed to decrease at a rate of 0.008 per year, based on a longitudinal study in a population of Swedish HF patients.<sup>18</sup> This assumption was also used in the recent Novartis submission to NICE for sacubitril–valsartan.<sup>7</sup> Trial utilities were modelled out to 5 years, after which a utility of 0.57 was applied for chronic HF based on a recent study in

the UK,<sup>19</sup> which was again decreased at a rate of 0.008 per year thereafter.

After 5 years, when trial utilities ceased to be applied and in order to avoid double counting, a disutility for each HF hospitalization of  $-0.1$  is applied to reflect the impact of hospitalizations on quality of life. This is similar to the disutility applied to hospitalizations from a previous cost-utility analysis for HF technologies,<sup>20</sup> Griffiths et al.,<sup>17</sup> and, more recently, the Novartis submission to NICE for single technology appraisal of sacubitril–valsartan.<sup>7</sup>

## Costs

As of autumn 2016, the cost of the device has not been released by the manufacturer as devices are not commercially available in Europe outside of use in clinical trials, and an implant procedure code is not available from the NHS. However, the authors have in this case assumed that the total cost of device acquisition and implant will be £12 000, based on the direct currency conversion from the average US MS-DRG payment (DRG 264 accompanied by the ICD-9-CM procedure code of 38.26: insertion of implantable pressure sensor without lead for intracardiac or great vessel haemodynamic monitoring), currently set at US\$17 750.

The cost of an implant complication is estimated as £1090, using a weighted average of the eight complications in the CHAMPION trial mapped to NHS reference costs.<sup>21</sup> The cost of standard HF care (excluding hospitalizations) is £36.31 per month based on previous estimates,<sup>17</sup> and is applied to stable HF patients in both cohorts. The cost of HF hospitalization is estimated from NHS reference costs as £2038, calculated as a weighted average of HF admissions.

## Sensitivity analysis

One-way sensitivity analysis was performed on the following parameters: HR for mortality reduction (0.55 to 1) from the lower bound of the 95% confidence interval (CI) from CHAMPION to 1 being no effect on mortality; HR for HF hospitalization (0.55 to 0.8) across the 95% CI from CHAMPION; cost of HF hospitalization (£1067 to £3884), from the lowest to highest costs of HF hospitalization in the NHS reference costs; and cost of implant procedure ( $\pm 25\%$ , £9000–£15 000).

A subgroup analysis of 119 patients in the CHAMPION trial with preserved EF ( $>40\%$ ) revealed that the treatment effect could be greater in these patients, reducing the hospitalization rate by 50%. This scenario was tested in the model.

The costs of HF hospitalization, implant complications, and monthly cost of treatment were acquired from several other European countries and the cohort model run using these inputs to simulate cost-effectiveness in other countries.

Probabilistic sensitivity analysis was performed using 1000 runs employing different estimates for the risks, HRs, costs, and utilities.

## Scenario analysis, including staff costs

A scenario analysis was also performed including the time spent on monitoring patients by a nurse (23–70 min per month). The lower bound of this range is from data collected by L.K. on CardioMEMS patients at his centre, and the upper bound is from a previous telemonitoring study using different technology.<sup>22</sup> Physician time was included at 7 min per month, again from early real-world data collected by L.K. at the University of California, San Francisco, Medical Centre. The costs for the time spent by nurses monitoring CardioMEMS

patients remotely is based on an hourly rate of £36 for a Band 5 nurse, and for doctors £105/h for a medical consultant.<sup>21</sup>

## Results

### Base case analysis

In the base case analysis over a time horizon of 10 years, PAP-guided HF therapy increased cost compared with usual care by £10 916 (i.e. from £6189 in usual care to £17 104 in PAP-guided HF therapy).

The model estimated a mean survival of 4.79 years for patients being treated with usual care practices and 5.17 years for patients with treatment guided by PAP monitoring, an increase of 0.38 years (Figure 2).

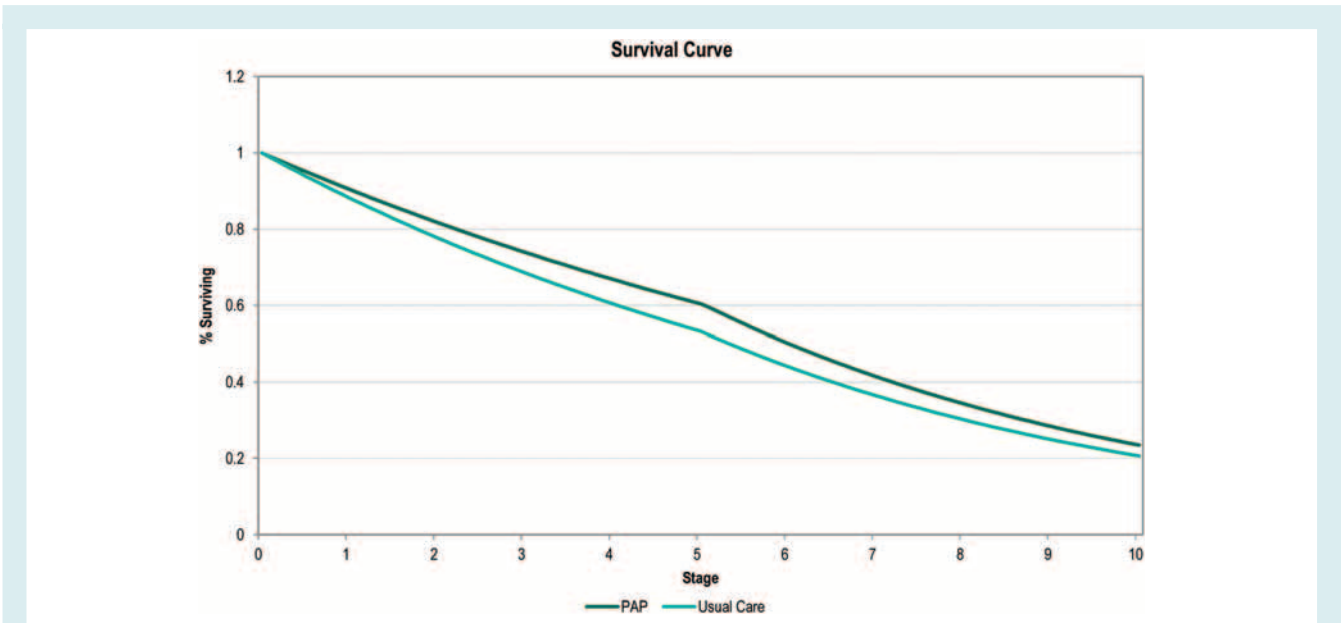
The QALYs per patient for usual care and PAP-guided patients were 2.57 and 3.14, respectively, reflecting an increase of 0.57 QALYs with PAP-guided treatment. The resultant ICER, the ratio between incremental costs and the QALYs, is estimated at £19 274/QALY.

### Probabilistic sensitivity analysis

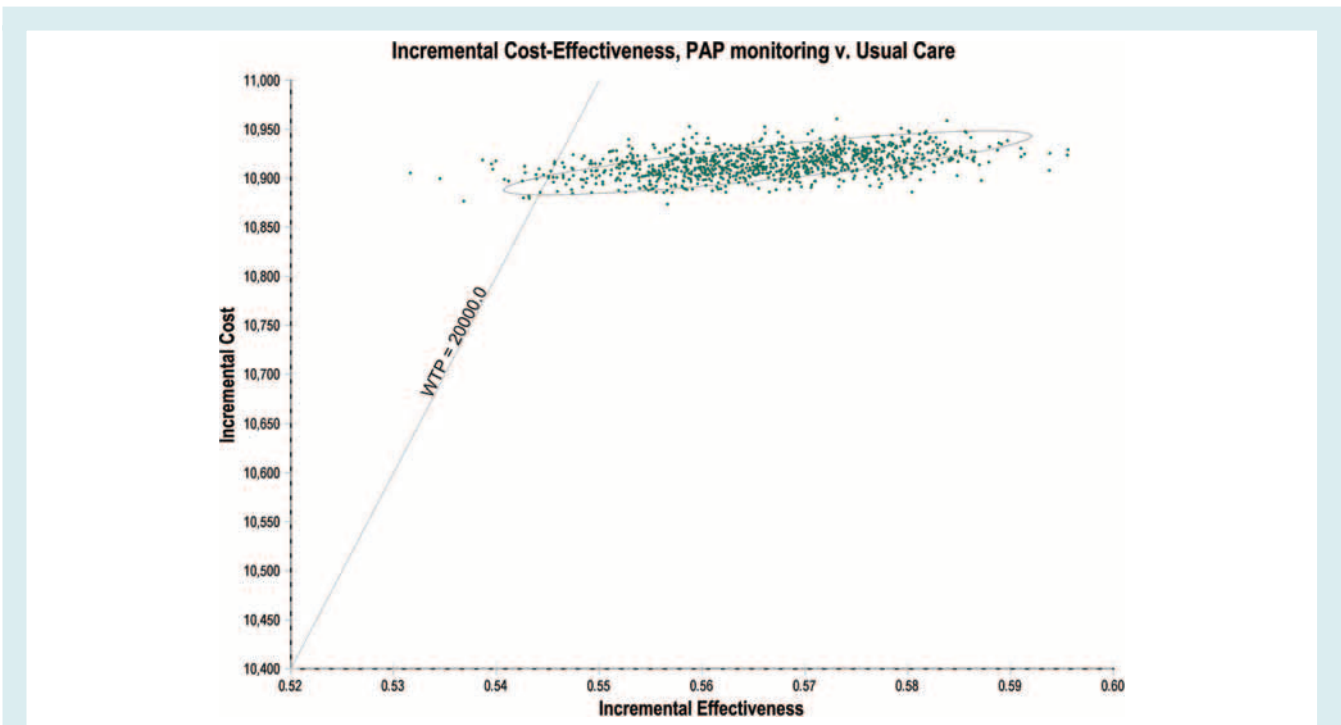
The results of the PSA displayed on a scatterplot (ellipse indicates 95% CI) show a tight cluster of results in the north-east quadrant. A line indicating a willingness to pay (WTP) threshold of an ICER of £20 000 has been drawn for reference (Figure 3); this line represents the WTP threshold below which NICE typically recommends a new treatment be made available to NHS patients. Almost all of the points on the scatterplot are underneath the line, as the probability of PAP being cost-effective at a WTP threshold of £20 000/QALY is 97.6%.

### Sensitivity analysis

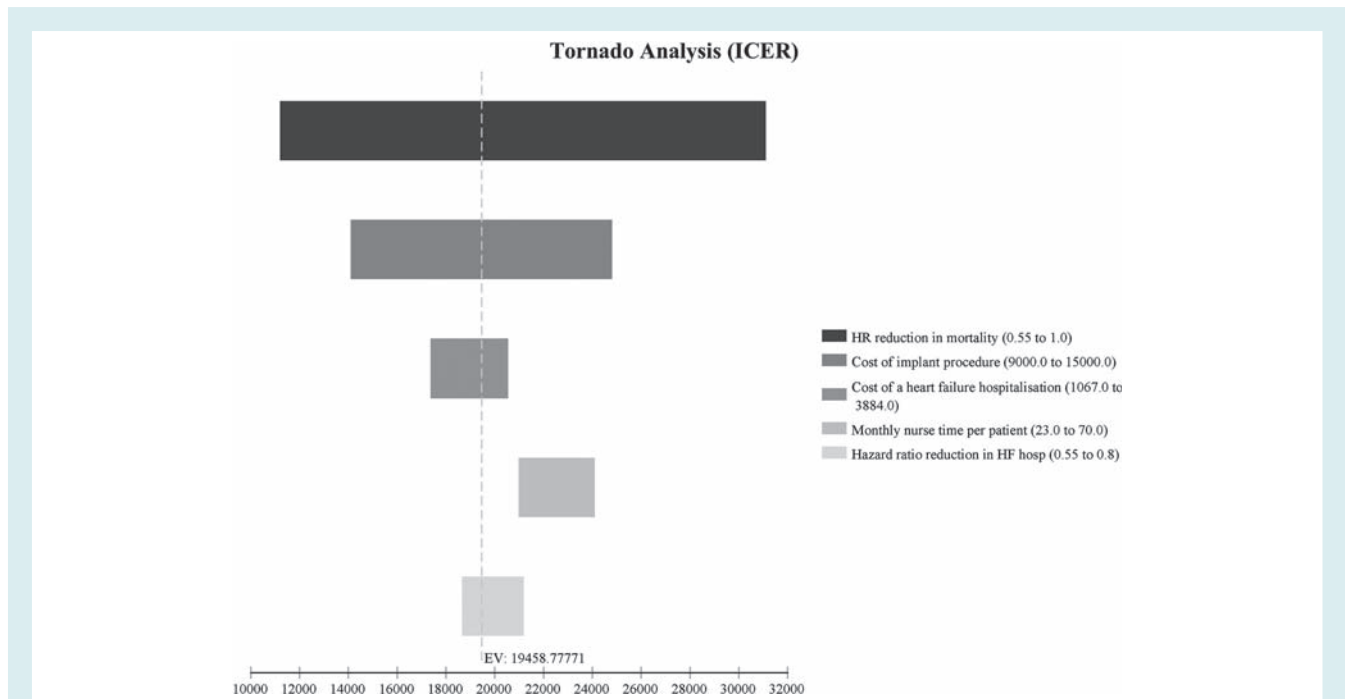
Sensitivity analyses performed do not substantially change the conclusions, as shown in Figure 4. Decreasing the mortality HR of PAP to 0.55 (from a base value of 0.8) resulted in an ICER of £11 205/QALY. This is due to a much greater difference in the expected QALYs between the PAP arm and the usual care arm when a lower HR was used. Similarly, increasing the mortality HR of PAP to 1 resulted in an ICER of £31 119/QALY. When the cost of the implant procedure was decreased to £9000 (from a base value of £12 000), the ICER went down to £14 106/QALY. Similarly, using a higher cost of implant procedure (£15 000) resulted in a higher ICER (£24 811/QALY). Decreasing the HF hospitalization HR of PAP to 0.55 (from a base value of 0.67) resulted in a lower ICER of £18 661/QALY. Again, this is due to a higher difference in the expected QALYs between the PAP arm and the usual care arm when a lower HR was used. Similarly, increasing the HF hospitalization HR of PAP to 0.8 resulted in a higher ICER of £21 191/QALY. When the cost of HF hospitalization was decreased to £1067 (from a base value of £2038), the ICER increased to £20 558/QALY. This is due to lower savings between the PAP arm and the usual care arm due to reduced HF hospitalizations when lower HF hospitalization



**Figure 2** Survival curve showing the number of patients alive in the model over time. At 5 years, when the mortality effect from CHAMPION is removed from the model, the mortality rate increases. PAP, pulmonary artery pressure.



**Figure 3** Cost-effectiveness scatter plot. Each of the dots on the scatter plot is one of 1000 mean cost and utility results of 20 000 model runs each with different input values sampled from the input distributions. PAP, pulmonary artery pressure; WTP, willingness to pay. The WTP = £20 000/QALY (quality-adjusted life year) is the typically accepted NICE (National Institute for Health and Care Excellence) threshold. Almost all of the samples (97.6%) fall under the WTP threshold, suggesting that CardioMEMS has a 97.6% probability of being cost-effective at that threshold.



**Figure 4** One-way sensitivity analysis. The results of the sensitivity analysis can be compared in this tornado diagram; a larger bar indicates a greater impact on the incremental cost-effectiveness ratio (ICER) or, in the case of mortality, indicates a wide range of uncertainty. The dotted line indicates the base case ICER. In the case of increased heart failure (HF) hospitalization costs the ICER is lower. HR, hazard ratio.

**Table 2** Comparison of costs and cost-effectiveness between countries

	UK	The Netherlands	Belgium	Italy	Germany
<b>Inputs</b>					
Cost of an implant complication	£1090	€2390	€1630	€3481	€2668
Cost of implant (includes device cost)	£12 000	€15 000	€15 000	€15 000	€15 000
Monthly cost to deliver medical care	£36	€99	€27	€148	€231
Cost of one hospital admission for HF	£2038	€4545	€2802	€4500	€4398
<b>Outputs</b>					
Modelled cost of usual care	£6189	€14 831	€7187	€17 556	€22 121
Modelled cost of PAP-guided therapy	£17 104	€27 472	€20 582	€30 483	€35 468
Incremental cost	£10 916	€12 641	€13 395	€12 926	€13 347
ICER	£19 274	€22 555	€23 899	€ 23 064	€23 814

HF, heart failure; ICER, incremental cost-effectiveness ratio; PAP, pulmonary artery pressure.

costs were used. Similarly, the ICER decreased to £17 370/QALY when the cost of hospitalization was increased to £3884.

When the model was run using the increased treatment effect found in the preserved EF patients, costs for the treatment group were reduced to £16 518 and the resultant ICER was £18 169.

### Comparison of model results in selected European countries

The model outputs were tested with cost inputs from four other European countries, The Netherlands, Belgium, Italy, and Germany. Comparative cost inputs and model outputs can be seen in Table 2. It should be noted that the clinical parameters were

unchanged. These analyses suggest that CardioMEMS is likely to be cost-effective in the countries selected.

### Scenario analysis, including staff costs

Scenario analysis performed, including the costs for nurses and doctors managing the data from the pressure monitors, increased the ICERs. When it was assumed that the time spent by a nurse monitoring each PAP patient is 23 min/month and that doctors spent 7 min/month per patient, the ICER increased to £22 342/QALY. If the time needed for nurses to manage these patients was assumed to be 70 min/month, the ICER increased to £25 464/QALY.

## Discussion

The results of our cost-utility analysis suggest that the CardioMEMS™ HF system could provide cost-effective benefits to HF patients in the UK: the base case ICER of £19 274/QALY is below the thresholds of £20 000–£30 000 per QALY used by NICE.

The CardioMEMS device differs from previous telemonitoring technologies in that it is the first system to provide real-time remote monitoring of PAP, with the goal of maintaining this pressure within a therapeutic range by adjusting medications in response to pressure trends. Previous remote monitoring systems have used non-invasive measurements such as weight, heart rate, and blood pressure communicated to physicians via telephone or data links, or data from cardiac implantable electronic devices implanted for therapeutic reasons (such as an implantable cardioverter defibrillator or CRT device).

Meta-analysis of several small studies of non-invasive remote monitoring suggested that such approaches may reduce HF hospitalizations and perhaps mortality,<sup>23</sup> but larger randomized trials have been neutral.<sup>24–26</sup> A UK cost-effectiveness analysis used modelling to compare structured telephone support where patients spoke to a human operator (usually a HF nurse), structured telephone support delivered by an automated machine, and remote monitoring of non-invasive measurements. Remote monitoring was superior in terms of cost-utility to either of the structured telephone support approaches, with an ICER of £9522/QALY gained over a lifetime horizon.<sup>20,27</sup>

A recent meta-analysis of remote monitoring of devices implanted for therapeutic reasons has suggested no change in mortality but a marked reduction in planned hospital visits, at the expense of an increase in unplanned hospital and emergency room visits.<sup>16</sup> The CardioMEMS system directly measures PAP, and may provide an earlier indicator of decompensation,<sup>28</sup> in addition targeting the haemodynamic congestion, rather than clinical congestion, targeted by traditional remote monitoring solutions. Besides being a new therapeutic target with drug therapies titrated to maintain PAP in a more normal range, the indicator showed improved efficacy under randomized conditions which is probably due to the physical parameter being monitored, i.e. PAP, being better able to detect early signs of acute decompensation. Furthermore, the CHAMPION trial only included patients who were at least moderately symptomatic (NYHA class III), and perhaps with a greater potential to obtain benefit in terms of reduced hospitalization and improved quality of life than the other studies which tended also to recruit patients with milder symptoms.

Others have estimated the likely cost-effectiveness of the CardioMEMS device in the American healthcare system. Sandhu and colleagues estimated an ICER of US\$71 462 per QALY gained.<sup>29</sup> The key differences, apart from the different costs of hospitalization in the different healthcare systems, are the assumptions relating to utilities. Sandhu *et al.* used the results of the disease-specific Minnesota Living with Heart Failure (MLWHF) assessments in the CHAMPION trial, converted to EQ-5D utilities using an algorithm, whereas the model presented here uses utility values derived directly from the EQ-5D assessments collected in

the CHAMPION trial because data quality (in terms of number of questionnaires completed) was much better for EQ-5D. Both models extend the utility effects beyond the trial period, but in our model we decrement the effect after the initial 12-month period, as previously described.<sup>17</sup> Both models ascribe disutilities to hospitalization. The MLWHF results display a much lower health-related quality of life in both the treatment and usual care cohorts and a reduced incremental effectiveness of treatment compared with that seen from the EQ-5D responses. Sandhu *et al.* thereby report incremental QALYs of 0.28 over a lifetime analysis, whereas our model estimates the incremental QALYs to be 0.67 over a 10-year time horizon.

Martinson *et al.* have also estimated the likely cost-effectiveness of CardioMEMS from the US perspective over a 5-year time horizon.<sup>30</sup> They report a base case of US\$29 593 per QALY using a payer perspective and using real-world claims data for the cost of a HF hospitalization in the USA (US\$16 770 for Medicare and US\$30 100 for private insurance) rather than an assumed cost of US\$12 832. They, like us, also did not map Minnesota scores across to health utility, but used the directly assessed EQ-5D scores for health-related quality of life.

The baseline mortality rate for HF in the usual care cohort was taken from previous work by Griffiths *et al.* in their model to estimate the cost-effectiveness of ivabradine as part of a submission to NICE.<sup>17</sup> They used the CARE-HF trial<sup>31</sup> to estimate age-related mortality and we assumed that there were enough similarities between that population and the target population for CardioMEMS to use the figures as an appropriate baseline risk of death. Although CARE-HF did not exclude NYHA class IV patients, the study population consisted of 94% NYHA class III patients. A total of 78% of CHAMPION patients had reduced EF at baseline, defined as <40%, compared with the CARE-HF inclusion criteria of <35% and a mean EF in that trial of 26%.<sup>32</sup> Baseline risk of hospitalization for the usual care cohort was from a meta-analysis of randomized trials of telemonitoring of implanted devices by Klersy *et al.*;<sup>16</sup> using this population probably underestimates the risk of hospitalizations and indeed the monthly risk of 3.5% used in the model is lower than the 5.8% calculated from the usual care cohort in the CHAMPION trial. We believe that this decision represents a conservative approach, and is likely to lead to an overestimate of the cost per QALY.

Recently, the first new disease-modifying therapy for HF treatment has been approved for use and is available for doctors to prescribe in many European countries. Sacubitril–valsartan is indicated in the UK for use in patients with class II–IV symptoms and an EF of <35%. We did not attempt to model the treatment effect of this drug within this model because at this time it is at an early stage of adoption and it would be difficult to estimate the proportion of patients in our modelled population who might already be taking it or begin taking it within the modelled time period. Additionally, the effects in class III patients with a prior hospitalization (the modelled population) are not clear. In the PARADIGM trial, the primary endpoint was not significant in the subgroup of patients in NYHA class III (HR 0.93, 95% CI 0.79–1.09) nor did the drug reduce HF hospitalizations significantly in this subgroup (HR 1.08%, 95% CI 0.88–1.34).<sup>33</sup> With these points in mind, we think that with

the data available it would be difficult to model reliably how CardioMEMS and sacubitril–valsartan would interact. This lack of data is a limitation to the model at this time.

The time spent monitoring the patient also influences our estimates of cost-effectiveness. Boyne et al. (TEHAF study)<sup>22</sup> estimated that the telemonitoring system used in their trial required 70 min a month (an average of 2 min 20 s per day) of nurse time to triage data from patients and to take any appropriate actions; it is important to note that the technology used in the TEHAF study and the instructions on how to monitor patients were both very different from the CardioMEMS™ HF system. There are very specific recommendations for dealing with the data from the CardioMEMS™ HF system and acting upon it. The selection of the time estimate from TEHAF was made in order to demonstrate the resource impact of a labour-intensive approach to monitoring. More recent experience over 18 months of using CardioMEMS in real-world clinical practice at a single centre in the USA has indicated that HF nurses spend on average 23 min per patient, per month. This time includes the time spent by the nurse reviewing the tracings, calling the patient with medication changes, ordering and checking the blood tests required, and discussing data and actions with the physician. The medication changes are made using an algorithm derived from the CHAMPION study, emphasizing the judicious use of diuretics and vasodilators, as well as maximization of guideline-based optimal medical therapy in patients with HF and reduced EF. The nurse spends an additional 10 min per month in documenting the medication changes in the electronic medical record. The physician spends on average 7 min per patient per month in reviewing the data with the nurses and setting up the treatment plan (Dr Liviu Klein, personal communication). We thought that a sensible approach to estimating the impact of introducing this technology in terms of human resources would be to use the data from Dr Klein's experience as the lower bound of a situational analysis and the figure from TEHAF as the upper bound. The ICER range of between £22 342 and £25 464/QALY indicates that the cost-effectiveness of the technology is affected by the time that staff spend managing the data. However, this estimate is somewhat crude at this point in time because the actual impact on resources remains unknown; for this reason we did not include staff time in the base case analysis of this model; however, when more accurate data become available it must certainly be part of any future modelling. For instance, it is not yet clear whether there are associated reductions in other patient management activities (such as clinic visits or general practitioner visits) which have not been recognized. Due to the uncertainty we see in estimating this important aspect of the mode, we recommend that resource utilization be studied as part of any future registry or clinical trial in the European healthcare setting.

A subgroup analysis of patients with preserved EF indicated the possibility of greater effectiveness in this difficult to treat population.<sup>34</sup> When the results from this analysis were used to inform the hospitalization rate in the model, the ICER decreased to £18 169. However, these results were based on only 22% of the enrolled CHAMPION population and should therefore be interpreted with caution.

All models and modelling analyses have to make assumptions and simplify reality in some way, which leads to limitations. The largest

area of uncertainty in the single RCT on CardioMEMS to date is the effect on mortality. Although the 20% beneficial effect on mortality in the CHAMPION trial did not reach statistical significance, this trend is included in our base case. This approach is standard practice in economic modelling which recommends the use of point estimates even when effect differences lack conventional statistical significance.<sup>35,36</sup> Readers may note that the full range of the CI for mortality from the CHAMPION trial has not been modelled but rather the HR is varied from the lower bound of the CI (0.55) to 1. The values above one and the wide range of the CIs reflect that the study was underpowered to detect mortality. However, if we were to model a HR for mortality above one we would be testing the assumption that the device increases mortality and the model would produce a negative ICER, indicating that it costs money to reduce outcomes. There is of course no suggestion to date that the CardioMEMS system would increase mortality. Uncertainty around the effect on mortality using a one-way sensitivity analysis shows that the ICER could be as high as £28 762 should the technology have no mortality benefit. Under this scenario, the higher ICER falls within the range of cost-effectiveness where NICE would require evidence of considerable clinical benefit before making a recommendation that the technology be made available to patients in England. We have tried to make conservative choices when faced with decisions on structure and assumptions throughout the modelling process. These include selecting a baseline hospitalization rate which is likely to be below that of the population of interest and only modelling trial based utility effects to 5 years.

Cost inputs collected from other European countries show that while cost of care varies between countries, the technology remains cost-effective within our model, with a range of €22 555–€23 899 per QALY. The new guidelines from the Heart Failure Association of the European Society of Cardiology<sup>14</sup> recommend that monitoring using the CardioMEMS system may be considered for patients with symptomatic HF with a previous HF hospitalization. Our model suggests that such an approach is likely to be cost-effective in the UK, at the currently considered threshold of value for money, and also in several other European countries.

## Conclusion

This analysis suggests that the CardioMEMS™ HF system could provide a cost-effective means for HF physicians to manage and treat patients outside of face-to-face clinic appointments, shifting care from hospital/clinic to home, reducing resource-intensive hospitalizations, and improving the quality of life of patients suffering from HF.

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