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STUDY DESIGN PAPER

Rationale and study design of the REM-HF study: remote management of heart failure using implanted devices and formalized follow-up procedures

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Aims We wish to assess the clinical and cost-effectiveness of remote monitoring of heart failure patients with cardiac implanted electronic devices.

Methods REM-HF is a multicentre, randomized, non-blinded, parallel trial designed to compare weekly remote monitoring-driven management with usual care for patients with cardiac implanted electronic devices (ICD, CRT-D, or CRT-P). The trial is event driven, and the final analysis will be performed when 546 events have been observed or the study is terminated at the interim analysis. We have randomized 1650 patients to be followed up for a minimum of 2 years. Patients will remain in the trial up to study termination. The first patient was randomized in September 2011 and the study is expected to complete in early 2016. The primary combined endpoint is time to first event of all-cause death or unplanned hospitalization for cardiovascular reasons. An economic evaluation will be performed, estimating the cost per quality-adjusted lifeyear, with direct costs estimated from the National Health Service perspective and quality of life assessed by the EQ-5D, Short-Form12, and Kansas City Cardiomyopathy Questionnaires. The study design has been informed by a feasibility study.

Conclusion REM-HF is a multicentre randomized study that will provide important data on the effect of remote monitoring-driven management of implanted cardiac devices on morbidity and mortality, as well as the cost-effectiveness of this approach.
Trial registration: UKCRN 10383.

Keywords Heart failure • Implanted devices • Remote monitoring • Care pathways • Randomized controlled trial

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Introduction

Up to 2–3% of the population have chronic heart failure (HF).[1] A recent study in England reported that one-third of people with HF have dyspnoea that severely limits physical activity,[2] and quality of life is poor relative to patients with other chronic conditions.[3] Approximately 2% of healthcare budgets in most developed countries are spent on HF management, with >60% of this related to the costs of hospitalization.[4] The UK National HF Audit most recently reported data from 92% of hospitals, with a mean duration of hospitalization of 13.1 days, and a death rate of 30% at 1 year.[5] Reduction in HF admissions is therefore key to reducing the overall cost of HF to the healthcare system.

An increasing proportion of patients with chronic HF have implanted electronic cardiac devices, such as an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT-P), or a combination of both (CRT-D). Such devices can collect information not only on device function and activity, but also on various physiological characteristics, including patient activity, transthoracic impedance, heart rate variability, nocturnal heart rate, and arrhythmia burden.[6] In England, the current implant rate for such devices is ~100–130 per million population.[7]

Investigators have considered the use of non-invasive monitoring technologies for remote HF management.[8,9] Moreover, several small studies have assessed the impact of remote monitoring of one or more physiological variables from implanted devices on patient and healthcare outcomes. Bourge *et al.* evaluated a remote monitoring strategy for 274 patients with HF using right ventricular haemodynamic data.[10] There was a non-significant reduction of 21% in HF-related events in those randomized to remote monitoring, with a significant 36% ($P = 0.03$) reduction in the secondary endpoint of HF-related hospitalization. More recently, the CHAMPION trial reported a 30% drop in the 6-month risk of HF hospitalization using remote monitoring of pulmonary artery pressure measured by an implantable sensor.[11]

Yu and colleagues retrospectively evaluated an implantable system capable of intrathoracic impedance monitoring in 33 patients with advanced HF.[12] Using an automated detection algorithm, an impedance drop below a threshold value was 77% sensitive in detecting hospitalization for fluid overload, with 1.5 false-positive (threshold crossing without hospitalization) detections per patient-year of follow-up. A larger observational study in 501 patients (SENSE-HF) reported a sensitivity of only 21% and a higher false-positive rate,[13] and a randomized controlled trial (DOT-HF) was stopped early due to slow recruitment after 335 patients were randomized, and reported a 79% increase ($P = 0.02$) in HF hospitalizations when the patient and the physician were 'alerted' to the crossing of a threshold of intrathoracic impedance.[14]

Retrospectively examining the clinical utility of a combination of physiological variables measured by implanted devices has suggested greater benefit from synthesizing information (and trends over time) from several variables rather than just relying on one variable. PARTNERS-HF reported that such use of data was able to stratify patients into low, medium, and high risk for decompensation (requiring hospitalization) in the next month.[6] More recently, Cowie and colleagues reported even better results from combining a larger number of data sets: monthly diagnostic evaluations in the high-risk group were 10 times more likely to have a HF hospitalization (event rate 6.8%) in the next 30 days compared with monthly evaluations in the low-risk group (event rate 0.6%).[15] Neither study prospectively tested whether such data could be used by healthcare professionals to reduce hospitalization safely and improve outcome.

The RAPID-RF (Remote Active Monitoring in Patients with Heart Failure) Registry is enrolling up to 1000 patients at 100 centres to evaluate the effect of 'alerts' from an implanted device, in combination with data on weight and symptoms collected from a linked external device.[16] Preliminary data suggest that the majority of alerts relate to weight rather than device-related information, and the predictive value has not been assessed. It uses only one manufacturer's technology and did not employ specific remote monitoring care pathways.

Recently, 716 HF patients in Germany with an implantable cardiac device were randomized to either home monitoring or usual care (IN-TIME Study). At 12 months, fewer patients had worsened HF in the remote monitoring group (19% vs. 28%; $P < 0.05$), and the mortality was also lower (3.4% vs. 8.7%, $P = 0.012$).

Remote monitoring using stand-alone technologies (external to the body) have also been examined in a number of randomized trials. Many of these trials were small, and although a recent Cochrane review[17] suggested benefit in terms of all-cause mortality and HF hospitalization, a more recent network meta-analysis did not confirm this.[18] Two recent large randomized trials have been neutral.[19,20] One large study in England, involving 3230 patients with diabetes, chronic lung disease, or HF, reported clinically important reductions in hospitalizations, emergency room admissions, and mortality,[21] but at a cost considered prohibitive at >£90 000 (€105 000) per quality-adjusted life year (QALY) when added to usual care.[22]

Prospective randomized studies of remote monitoring of HF patients using implantable devices have not been of adequate size or duration to assess the clinical and cost-effectiveness of such an approach robustly in a general healthcare setting. The REM-HF (REmote Monitoring: an evaluation of implantable devices for management of Heart Failure patients) Study has been designed to address these issues, and is based on personalized care informed by remote monitoring of patient activity, arrhythmia burden, and potential signs of decompensation from implanted devices, using specifically trained remote monitoring staff working to pilot-tested guidelines. The remote monitoring staff interact closely with the clinical teams caring for the patients at the nine hospitals in England which will recruit to the study.

Study design

The feasibility study

A feasibility study was used to plan the REM-HF study: 80 HF patients in two cohorts were recruited from one tertiary care centre (Southampton, UK). Patients had ICDs or CRT-Ds. Patients recruited to the feasibility study were stable, on optimal tolerated medical therapy for at least 6 weeks prior to recruitment, and had

Table 1 Clinical features of those patients enrolled in the two cohorts of the feasibility study for REM-HF

	Cohort 1 ($n = 40$)	Cohort 2 ($n = 40$)	*P*-value
Average age (years) (mean ± SD)	70.7 ± 7. 7	70.4 ± 7.2	0.82
Male (*n*, %)	36 (90%)	38 (95%)	0.40
Ischaemic aetiology (*n*, %)	19 (48%)	22 (55%)	0.50
Previous CABG (*n*, %)	16 (40%)	17 (42%)	0.82
Previous PCI (*n*, %)	6 (15%)	6 (15%)	1.0
Previous MI (*n*, %)	24 (60%)	28 (70%)	0.35
Angina (*n*, %)	13 (33%)	14 (35%)	0.81
Diabetes (*n*, %)	11 (27%)	10 (25%)	0.80
LVEF (%) (mean)	38	38	
Hypertension (*n*, %)	14 (35%)	27 (67%)	0.004

CABG, coronary artery bypass graft; MI, myocardial infarction.

the ability independently to comprehend and complete the quality of life questionnaires. Exclusion criteria were inability to consent, awaiting heart transplantation, life expectancy of <1 year in the opinion of the clinician, or a current device-related complication. Cohort 1 was only observed, whereas Cohort 2 was used to explore the utility of remote monitoring of implantable device technologies in HF management, and staff workload issues. Patient demographics are summarized in *Table 1*. Remote monitoring was used as an 'add on' to usual care provided by the multidisciplinary HF team. Of all patients approached, 83% consented to take part in the feasibility study, and there were no drop-outs during the 6-month follow-up period.

The 40 patients in Cohort 2 (remote care pathway) were randomized 1:1 to either daily or weekly monitoring for 3 months, with all patients monitored weekly for the final 3 months of the study. In the event of data from the implantable device suggesting a need for a change in patient management, the patient and the responsible primary care practitioner were telephoned. If subsequent data indicated a poor response to the suggested change in management, the patient was then invited to the hospital clinic for a face-to-face review. Remote data downloads were reviewed for both device functionality and disease state [arrhythmia burden, non-sustained ventricular tachycardia (VT), sustained VT requiring therapy, AF episodes, heart rate variability, activity data, and thoracic impedance data]. 'Alert' facilities capable of signalling potential deterioration in patient clinical status or the device system were programmed 'on' but could be switched off according to the clinical judgement of the cardiologist with responsibility for the patient. If an alert was triggered, the patient could hear the audible alarm and then contacted the study monitor and performed a remote data download; the monitor informed the responsible attending senior clinician of the data transmission and he or she then determined the appropriate clinical action.

In the event of clinical deterioration (but not severe enough to necessitate emergency admission), patients contacted the monitor and performed a data download. The monitor then gave the patient a management plan in the light of the available information, with appropriate support from the primary care team to ensure implementation within one working day. In the event of an emergency, the patient accessed emergency services in the usual way.

All healthcare contact was entered in a study-specific diary by the patients. Monitoring staff and the patient's cardiologist recorded all study-related activity in the patient's electronic health record. In addition, all patients completed a generic health-related quality of life questionnaire (SF-36, short version) and a disease-specific questionnaire (Minnesota Living with Heart Failure questionnaire) at enrolment and 6 months.

With 83% of patients approached regarding the feasibility study consenting to take part, and with no drop-outs at 6 months, we considered a larger adequately powered study to assess clinical and cost-effectiveness. It was also clear that one remote monitor could handle the work related to monitoring of 200 patients within a standard working week. The approach used in the feasibility study was used in the design process for the main study, the development of the procedures handbook, and the data collection system. It was critical to developing the role of the remote monitoring staff in guiding patient care in the community.

REmote Monitoring: an evaluation of implantable devices for management of Heart Failure patients

Study design

REM-HF is a multicentre, randomized, non-blinded, parallel group study. The trial is registered with the National Institute of Health Research in the UK (Trial no. 10383). Patients are randomized in a 1:1 ratio to optimal medical management (usual care) or optimal medical management informed by weekly remote monitoring of the data from their implanted device. The study is event driven, with a sample size of 1650 patients [Thus $P = 0.05$ and power >90% with a maximum hazard ratio (HR) of 0.755 and maximum of 5% withdrawals]. The first patient was randomized in September 2011 and the study is expected to finish in early 2016. The average follow-up time will depend on the speed of patient recruitment and the event rate, but is anticipated to be ~32 months. Minimum follow-up will be 24 months, and maximum ~42 months.

Objectives

The primary study endpoint is the survival time to first event of all-cause death or unplanned hospitalization for cardiovascular reasons (at maximum HR 0.755), as assessed by the Endpoint Review Committee (Appendix 1) using data from primary and secondary care records, coroner reports, and the death certificate.

Secondary endpoints are combined cardiovascular mortality and cardiovascular hospitalization, HF hospitalization, and cost-effectiveness. The main outcome measure in the economic

evaluation will be cost per QALY, with quality of life assessed using the EuroQol (EQ5D), Short-Form 12 (SF-12), and Kansas City Cardiomyopathy Questionnaire (KCCQ). Costs will be measured using an NHS perspective. As part of the study, we will record the costs associated with providing remote monitoring, as well as any routine cardiac care received in each group. Resource use will be obtained from a variety of sources as appropriate, including hospital records and directly from participants. We will follow National Institute for Health and Care Excellence (NICE) guidelines (Modified Client Services Inventory) for economic evaluation.

Patients

The intended study population for this study is patients with HF and an implanted cardiac device (ICD, CRT-D, or CRT-P) that can be monitored remotely. Eligible subjects meeting the inclusion and exclusion criteria (detailed below) at nine English hospitals will be considered for the study.

Inclusion criteria

Participants will all have received an implantable device at least 6 months previously (to allow for system stabilization) that is set-up for the treatment and monitoring of chronic HF. Patients receiving these devices will be doing so according to clinical requirement and UK guidance from NICE, and not for the purposes of this study. All patients will have symptomatic HF (NYHA class II–IV) documented at the time of study enrolment. In addition, recruited patients will have been on stable medical therapy for HF for at least 6 weeks prior to recruitment, have the ability independently to comprehend and complete the study health-related quality of life questionnaires, have the ability to give informed consent, be on optimal medical therapy according to the treating physician and the applicable professional guidelines (NICE), and have had their device programmed to give optimal therapy according to the treating physician.

Exclusion criteria

Participants will be excluded from the study if they are unable to use the remote monitoring download technology due to mental or physical limitations, are less than 18 years old, pregnant, awaiting heart transplantation or have a life expectancy of <1 year due to non-cardiovascular disease in the opinion of the treating physician, have current device-related complications, device change, or lead replacements within 30 days, or acute myocardial infarction or

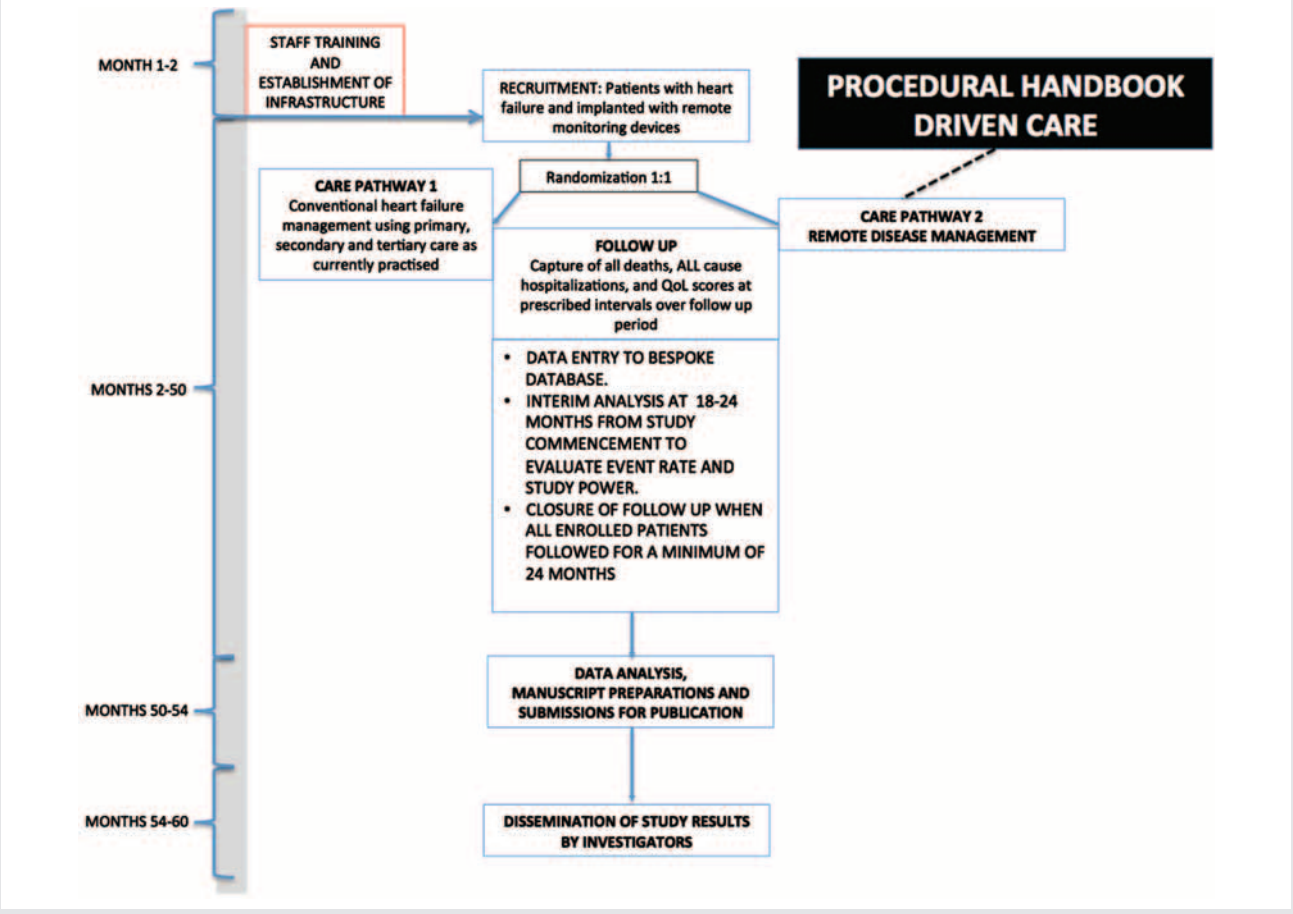

Figure 1 Study Flowchart

coronary intervention/coronary artery bypass grafting within 3 months.

Patient randomization

This will be performed centrally via a study-specific electronic case report form management system, using a randomization schedule that is stratified by recruiting site, with randomly permuted blocks of four and six patients.

Study plan

The study schedule is shown in *Figure 1*. All patients will be followed-up for a minimum of 24 months.

Intervention

Remote care pathway

The remote-monitoring informed care pathway was developed from our experience in the feasibility study, informed also by literature and guideline review.[1] The REM-HF steering group (Appendix 1) agreed the operational procedures which governed the actions of remote monitors in response to data. A formalized 'Procedural Handbook' comprehensively dealt with HF, arrhythmia, and device management, indicating what changes would be likely to be necessary in response to changes in remotely collected data. The site remote monitor was responsible for co-ordinating such changes, with physician support as necessary, using telephone, primary care, or direct patient review in secondary/tertiary care.

Usual care pathway

Usual care pathways will differ somewhat between centres, although all operate under NICE recommendations. Remote device follow-up for technical checks is currently performed, usually 3 or 6 monthly, in all centres. This 'usual' device care will be unaffected as the study assesses the value of weekly pre-emptive monitoring of disease state and not routine device technical follow-up.

Quality of life assessment

All participants will complete the health-related quality of life questionnaires SF-12, EQ5D, and the KCCQ at enrolment, at 3, 6, 12, and 24 months, and at the end of the study. The initial quality of life questionnaires will be completed at the time of patient enrolment in the hospital. Subsequent assessments will be performed by the patients in their homes. The forms will be sent to them by post with a pre-paid return-addressed envelope to facilitate the return of completed forms. Receipt of the forms and their return will be managed by the study administration staff.

Interim analyses

An Independent Data and Safety Monitoring Committee will review recruitment, data completeness, and endpoints, and ensure no adverse effects from remote monitoring, at appropriate time points during the study. There will be one interim analysis at 400 primary endpoints.

Statistical considerations

The primary analysis will be performed on adjudicated endpoints in the intention-to-treat population (all randomized patients), following a group sequential design. The interim analysis and the final analysis will consist of a two-sided log-rank test comparing the control and intervention groups.

The null hypothesis is that the time to first event in the intervention group is identical to the time to first event in the control group. The alternative hypothesis is that the time to first event in the intervention group is different from the time to first event in the control group. To maintain study blinding, the statistician of the Data and Safety Monitoring Committee will link the time to event data at the interim analysis to the randomization code, calculate the log-rank statistic, and compare it with pre-defined limits. Kaplan–Meier curves will be used to visualize survival data.

Secondary analyses

Secondary endpoints will be analysed according to the type of scale. Time-to-event endpoints will be analysed in the same ways as the primary endpoint; dichotomous variables will be analysed by a likelihood χ^2 test; continuous endpoints will be analysed by analysis of covariance, including the baseline value as a covariate if available; variables with a right-skewed distribution within random groups will be log-transformed prior to analysis. All secondary endpoint comparisons will be performed at $\alpha = 0.05$, without adjustment for multiplicity. Extended analyses will be conducted using regression models (linear, logistic, or Cox proportional hazards) to explore further the influence of patient characteristics and clinical conditions on outcome. The list of such variables includes age, gender, site, co-morbidities, type of device, NYHA class, ischaemic/non-ischaemic HF, and underlying cardiac rhythm (AF vs. sinus rhythm).

Sample size

The study is designed to demonstrate a 20% reduction in the primary endpoint with an overall type 1 error rate of 5% (two-sided) including one interim analysis, and with a power of 90%. Based on data from COMPANION[23] and CARE-HF[24] trials, with a patient population comparable with that of this study, we conservatively assume an event rate of 40% at 24 months. Accordingly, a minimum of 546 events will be observed if the study is not stopped at the interim analysis. To reach that goal, a range of possible recruitment and follow-up scenarios have been considered. We have now recruited 1650 patients over an 18-month period, who will have minimum of 24 months follow-up, allowing for a 5% drop-out rate, and the use of multifactorial rather than unifactorial modelling. We are confident that the expected drop-out rate is a realistic estimate from our feasibility analysis.

Ethics and monitoring

The Steering Committee is responsible for the clinical and scientific conduct of the study and the publication of the results. An independent Endpoint Review Committee reviews and adjudicates all pre-specified events according to established definitions. Both committees only have access to blinded data while the study is underway. An independent Supervisory Committee oversees the study and an independent Data and Safety Monitoring Committee reviews the interim analysis. Members of the committees are listed in Appendix 1. The trial design was approved by the relevant Research Ethics Committee. The trial is being conducted in accordance with UK laws, Good Clinical Practice, and the Declaration of Helsinki 2002.

Discussion

The ready availability of remote monitoring technologies in many HF patients in developed countries raises the possibility of improving outcome and reducing healthcare costs. However, the evidence base for the benefits (and disadvantages) of adopting such an approach is weak. Frequent pre-emptive remote monitoring by implantable devices may enable early identification and treatment of pulmonary congestion and malignant arrhythmias (the two main mechanisms for mortality in HF), which could reduce HF morbidity and related hospitalization.[25]

The care model and technologies used in this trial will offer personalized healthcare through remote patient management in the community, using secondary and tertiary care expertise and interventions as required. Our pilot study showed that remote monitoring is readily accepted (and continued) by patients who have an implantable cardiac electronic device. Weekly remote monitoring is feasible for healthcare professionals trained to undertake such a task, and we wish to test the clinical and cost-effectiveness of this approach when applied to a large number of individuals at nine English hospitals, with varying types of clinical service.

Redesigning care pathways to incorporate remote monitoring is not straightforward, and before doing so the clinical community wishes to see robust clinical effectiveness evidence from large randomized trials. We believe that REM-HF will provide such evidence, and that its cost-effectiveness data will inform new reimbursement models that are essential for the optimal deployment of monitoring technologies in an increasingly challenged healthcare environment.

Conclusions

REM-HF is an important randomized controlled trial that will assess whether weekly remote monitoring of data collected from implantable cardiac electronic devices in patients can reduce mortality and morbidity in patients with chronic HF, compared with usual care. In addition, it will provide an assessment of the value for money of this approach. The results of the REM-HF study will provide further clarification of the benefits of remote monitoring in patients with HF, and may have important implications for the individualized therapeutic strategies targeted at reducing the risk and consequences of arrhythmia and decompensation for those living with the syndrome, and the way we organize HF care within the healthcare systems.

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Conflicts of interest: J.M.M. reports grants from Medtronic, St Jude Medical, and Boston Scientific, during the conduct of the study; grants and personal fees from Medtronic, grants and personal fees from Boston Scientific, grants from St Jude Medical, and personal fees from SORIN, outside the submitted work. J.G. reports grants from St Jude, outside the submitted work. S.K. reports grants from Medtronic, St Jude Medical, and Boston Scientific, during the conduct of the study. G.A.N. reports grants, personal fees, and non-financial support from St Jude Medical, grants and non-financial support from Boston Scientific, and personal fees from Medtronic, outside the submitted work. J.M.McC. reports grants from St Jude Medical, during the conduct of the study. K.K.W. reports grants from Medtronic UK, outside the submitted work. D.J.W. reports grants from Boston Scientific, personal fees from Boston Scientific, Medtronic, and St Jude, and other fees from Boston Scientific and Medtronic, outside the submitted work. M.R.C. is currently conducting research funded by Boston Scientific, Medtronic, and St. Jude Medical. He has received consultancy fees, honoraria, and travel expenses for lecturing at scientific meetings from each of these companies. All other authors have no conflicts to declare.

Appendix 1. Committee and Board Members

Steering Committee

John Morgan (Southampton, UK, Co-chair), Martin R Cowie (London, UK, Co-chair), Jas Gill (London, UK), Sue Kitt (Southampton, UK), Andre Ng (Leicester, UK), Janet McComb (Newcastle, UK), Alison Seed (Blackpool, UK), Simon Williams (Manchester, UK), Klaus Witte (Leeds, UK), D. Jay Wright (Liverpool, UK).

Endpoint Review Committee

Guy Haywood (Plymouth, UK), Adrian Rozkovec (Bournemouth, UK), George Sutton (London, UK).

Data and Safety Monitoring Committee

Henry Dargie (Glasgow, UK, Chair), Professor Ian Ford (Glasgow, UK), Richard Charles (Liverpool, UK).

Supervisory Committee

John Camm (London, UK, Chair), Jeremy Pearson (British Heart Foundation, London, UK), John Cleland (London, UK), Seah Nisam (Diegem, Belgium).

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