TECHNOLOGY ASSESSMENT REPORT COMMISSIONED BY THE NIHR HTA PROGRAMME ON BEHALF OF THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DRAFT PROTOCOL

1 TITLE OF THE PROJECT

Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block, part review of Technology Appraisal 88

2 TAR TEAM AND PROJECT 'LEAD'

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3 PLAIN ENGLISH SUMMARY

Bradycardia is a term used when a person has an unusually slow heart rate (<60 beats per minute). The rate of the heart beat is regulated by the sinus node, which is the heart's natural pacemaker. The sinus node is made up of a group of impulse-generating cells in the top right chamber of the heart. Malfunction of the sinus node can lead to an irregular heart rate, and can be a cause of bradycardia. A term used to capture conditions resulting from irregular heart rate due to problems with the sinus node is sick sinus syndrome (SSS). Bradycardia can also be caused by problems with the electrical impulses between the upper (atria) and lower (ventricle) chambers of the heart, which is called atrioventricular (AV) block. Common symptoms of bradycardia include feeling lightheaded, dizzy, and more tired than usual, finding it harder to exercise, and even fainting. To relieve symptomatic bradycardia, the decision might be taken to implant an artificial pacemaker. Artificial pacemakers are small

battery driven devices that are implanted in the chest. Pacemakers are fitted with wires (called leads) that have sensors that detect the natural heartbeat, or lack thereof, and then send that information to a small computer in the pacemaker. The pacemaker uses this data to send signals back to the heart to help the heart beat regularly. There are several different types of pacemakers. Some pacemakers are connected to only one chamber of the heart (single chamber pacemakers), whereas others are connected to two chambers (dual chamber pacemakers). The type of pacemaker implanted is based on the underlying condition causing the irregular heart rate and the person's age. Most people who need a pacemaker implanted are older than 60 years of age.

The aim of this project is to assess the benefits and risks of dual chamber pacemakers compared with single chamber pacemakers for patients with bradycardia caused by SSS, but without AV block. In addition, this project will include an assessment of whether these pacemakers are likely to be considered good value for money for the National Health Service (NHS). This is a part review of Technology Appraisal 88 (Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block).[1] All other recommendations in TA88 will remain extant.

4 DECISION PROBLEM

4.1 Aim

The aim of this Multiple Technology Appraisal (MTA) is to appraise the clinical and cost-effectiveness of dual chamber pacemakers for treating symptomatic bradycardia in people with sick sinus syndrome (SSS) in whom there is no evidence of impaired atrioventricular conduction, and to update the recommendations of Technology Appraisal 88 (TA88) in relation to this indication.

4.2 Background

4.2.1 Bradycardia

Bradycardia is a term used for unusually slow heart rate (<60 bpm). Pathological bradycardia can be caused by conditions affecting the electrical conduction system of the heart, including sick sinus syndrome and atrioventricular (AV) block.[2] Bradycardia may be asymptomatic, but people can also present with dizziness, fatigue, exercise intolerance or syncope (fainting).

4.2.2 Sick sinus syndrome

SSS is caused by dysfunction of the sinus node, the heart's natural pacemaker. The sinus node consists of a cluster of cells that are situated in the upper part of the right atrium (the right upper chamber of the heart). The sinus node generates the electrical impulses which are

conducted through the heart stimulating it to contract. SSS covers a spectrum of arrhythmias with different underlying mechanisms, manifested as bradycardia, tachycardia (fast heart rate) or a mix of the two.[2] The most common cause of SSS is idiopathic degeneration or scarring of the sinus node with increasing age. However, SSS can also be caused by some types of medication, such as calcium channel blockers and beta blockers, or by diseases and conditions that cause scarring or damage to the heart's electrical system, such as ischaemic heart disease, heart failure and heart valve disorders.

4.2.3 Atrioventricular block

In AV block or heart block, the electrical impulses from the sinus node in the right atria to the ventricular chambers are slowed or blocked at the AV node or within the His Purkinje system, which conducts electrical impulses between the atria and ventricular chambers. Although heart block can be present at birth (congenital), people are more likely to develop the condition, with the risk increasing with age, along with the incidence of heart disease.

4.2.4 Diagnosis

Symptoms of SSS and AV block are usually non-specific and often observed in other disorders, such as dementia in elderly patients, which makes it difficult to diagnose.[3] Diagnosis is made by considering a patient medical history and symptoms, and through the use of electrocardiograms (ECGs). The ECG abnormalities may be intermittent. Therefore longer ECG monitoring, with Holter monitoring (ECG monitoring for 24–48 h) or event recorders, could allow symptom rhythm correlation and accurate diagnosis of symptoms. [3]

4.2.5 Pacemakers

Pacemakers are small battery driven devices which regulate abnormal heart rhythms. A pacemaker consists of a small generator and one or more leads which are connected to the heart. The leads will sense the heart’s electrical activity and, when it becomes too slow, an electrical impulse from the generator will initiate the contraction of the heart.

Single chamber pacemakers have one lead which is attached either to the atrium (atrial pacing) or the ventricle (ventricular pacing). Dual chamber pacemakers have two leads; one attached to the atrium and the second to the ventricle.

The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) have established nomenclature to describe the different pacing modes of pacemakers, which comprises a four-letter combination (Table 1).[4] The first letter indicates which chamber or chambers are paced, and the second letter specifies which chamber(s) are sensed. Letter I and II are usually, but not necessarily, the same. The third letter is inherently linked to letter II and describes the mode of response to sensing. The

pacemaker can be: inhibited (I), if it senses a spontaneous depolarisation; triggered (T), if it senses that no depolarisation has occurred (uncommon); and both inhibited and triggered (D).

Table 1: Definition of Generic Anti-bradycardia pacing codes (NASPE/BPEG)[4]

Position	I	II	III	IV
Category	Chamber paced	Chamber sensed	Response to Sensing	Rate modulation
Codes	A = Atrium V = Ventricle D = Dual (Atrium and Ventricle)	A = Atrium V = Ventricle D = Dual (Atrium and Ventricle)	O = None T = Triggered I = Inhibited D= Dual (Triggered and Inhibited)	O = None R = Rate-modulated

In an AAI or VVI pacemaker, the pacemaker senses an atrial or ventricular event and withholds its signal. DDI pacemakers will inhibit the output of the device in either chamber where it senses a signal. The most common example of the letter D in the 3rd position is in DDD pacemakers, which have dual functionality. On sensing an atrial signal, the DDD pacemaker initially inhibits the atrial output, which triggers a timer that, after a set time interval, initiates a ventricular output. If the DDD device senses a ventricular signal during the triggering interval, the pacemaker also inhibits the ventricular output. The fourth letter specifies whether the pacemaker is programmed to sense and increase the heart rate in response to physical, mental or emotional activity. Rate responsive pacemakers control heart rate by sensing body movement and/or breathing.

After pacemaker implantation, there are a number of programming options available to physicians including: pacing mode; lower rate; pulse width and amplitude; sensitivity; and refractory period. Dual chamber pacemakers may have additional features such as maximum tracking rate, AV delay, and mode switching algorithms for atrial arrhythmias.[5]

4.2.6 Implant procedure and follow-up

Pacemakers are usually implanted under local anaesthetics. A small incision is made below the collarbone to facilitate lead implantation and a small pocket created under the skin to hold the pacemaker device. The pacing lead is inserted in to the heart through a major vein. One end of the lead is securely lodged in the tissue of the heart and the other end is connected to the pacemaker. The position of the lead is checked using X-ray imaging. Testing and programming of the pacemaker is done wirelessly and can be changed at any time. The hospital stay is usually brief and the implant procedure could be carried out as day surgery or

might require a single overnight stay in the hospital. Implantation of a dual chamber pacemaker may take longer than a single chamber pacemaker, because dual chamber pacemakers require the insertion and placement of two leads. The requirement for an additional lead in dual versus single chamber pacemakers might lead to an associated increased risk of complications, such as lead displacement.[6]

People with permanently implanted pacemakers require regular follow-up to check: the function of the pacemaker leads; the frequency of utilisation and the battery life of the pacemaker; and for abnormal heart rhythm.[7] The battery life of a pacemaker is around five to eight years; following which replacement of the pacemaker will be required. To replace it an incision is made over the previous site of insertion, the old pacemaker generator is removed and a new one attached to the existing lead(s). Problems with pacemaker leads, such as loss of contact between the lead and the heart, are rare, but require re-operation. Where repair of a fault with a lead is necessary, the old lead may be left in place but disconnected from the pacemaker and a new lead implanted. Removal of old leads can be complicated by the formation of scar tissue connecting the lead to the vein and/or the heart.

4.2.7 Complications

Most complications occur during or soon after implantation of a pacemaker. Some of the more common complications are lead displacement (1.4%) and puncture of the lung when placing the leads, which can lead to pneumothorax (1.9%) or haemothorax.[8] One of the most serious, but rarer, complications that can arise during the implant procedure is cardiac perforation. There is also the risk of infection of the pacemaker pocket or the leads.[9] Complications occurring at a later date mainly involve dysfunction of the pacemaker or of the leads, that is, failure to pace or sense appropriately. Other late complications include infection or erosion of the pacemaker site or its leads.[9]

Reoperation may be required as a result of a complication, such as lead displacement, infection or pacemaker erosion, but it can also be due to a need for pacemaker upgrade (single to dual) or pacemaker replacement due to changed clinical needs, or end of battery life.[6] The complication rate associated with a reoperation is substantially higher than that associated with initial implantation.[10]

4.3 Place of the interventions in the treatment pathway

4.3.1 Clinical Guidance

NICE TA88 (2005) recommends dual chamber pacemakers for patients with symptomatic bradycardia which is due to SSS, AV block, or a combination of the two.[1] However, there are a few exceptions in which single chamber atrial or ventricular pacemakers are preferred:

- single chamber atrial pacemakers for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction;

- single chamber ventricular pacemakers for patients with AV block with continuous atrial fibrillation;

- single chamber ventricular pacemakers for patients with AV block alone, or in combination with SSS, when patient-specific factors, such as frailty or the presence of comorbidities, influence the balance of risks and benefits in favour of single-chamber ventricular pacing.

Similarly, the guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA), published in 2008, recommend dual chamber pacemakers for AV block and for SSS if there is a suspected abnormality of the atrioventricular conduction or an increased risk for future atrioventricular block.[5] Single chamber ventricular pacemakers are recommended for patients with AV block and chronic atrial fibrillation or other atrial tachyarrhythmias, and single chamber atrial pacemakers are recommended for patients with SSS but no suspected abnormality of the AV conduction and who are not considered to be at increased risk for future AV block.

In 2013, the European Society of Cardiology (ESC) published their guidelines on cardiac pacing and cardiac resynchronization therapy.[11] ESC recommends dual chamber pacemakers as a first choice for patients with SSS and/or AV block, with the exception of patients with persistent AV block and continuous atrial fibrillation for whom a single chamber ventricular pacemaker is recommended.

The differences in recommendations between the more recent ESC guidelines and those of NICE and the ACC/AHA are linked to the completion and publication of the DANPACE trial,[12] which has provided new evidence on the comparison of single chamber atrial pacing with dual chamber pacing in SSS with no evidence of AV block. One of the objectives of this MTA is to establish whether any other evidence has been identified in this area.

4.3.2 Current clinical practice

The prevalence of bradyarrhythmias due to SSS or AV block requiring permanent pacemaker implant is unknown.[11] However, in 2011 the implant rate of new pacemakers in the UK was ~500 per million people in the population.[13] Of these, the majority were dual chamber pacemakers (69%), ~30% were single chamber ventricular pacemakers and less than 1% were single chamber atrial pacemakers. The most common modes of pacing were DDDR (66.9%) and VVIR (29.8%).

4.4 Scope

This report will review the evidence on the following PICO:

Population

People with symptomatic bradyarrythmias due to SSS without AV block.

Intervention

Permanent implantable dual-chamber pacemakers.

Comparator

Permanent implantable single-chamber atrial pacemakers.

Outcomes

- Mortality (all cause);
- Heart failure;
- Atrial fibrillation;
- Stroke;
- Exercise capacity;
- Cognitive function;
- Requirement for further surgery;
- Adverse effects of pacemaker implantation (including peri- and post-operative complications, atrial fibrillation and device replacement);
- Health-related quality of life (HRQoL).

5 REPORT METHODS FOR SYNTHESIS OF EVIDENCE OF CLINICAL EFFECTIVENESS

The MTA will be undertaken following the general principles recommended in the PRISMA statement (formerly the QUOROM statement).[14]

5.1 Search strategy

To identify relevant randomised controlled trials (RCTs), multiple electronic databases will be searched, including MEDLINE, EMBASE, and The Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], Cochrane Central Register of Controlled

Trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment Database [HTA database]). Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions provided by manufacturers will be assessed for unpublished data.

No language restrictions will be applied to the search strategy. Full details of the terms used in the scoping search are presented in Appendix 9.1.1. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

5.2 Study selection criteria

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 2). It is anticipated that relevant manufacturers will provide submissions that may include unpublished data that will be considered. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained and the relevance of each study assessed. If a study is only reported as a meeting abstract or if full paper manuscripts cannot be obtained, the study authors will be contacted to gain further details. Studies for which insufficient methodological details are available to allow critical appraisal of study quality will be excluded. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 2. Inclusion criteria

Study design	Randomised controlled trials of parallel or cross over design
Population	People with symptomatic bradycardia due to sick sinus syndrome without atrioventricular block
Intervention	Permanent implantable dual-chamber pacemakers
Comparator	Permanent implantable single-chamber atrial pacemakers

5.3 Data extraction strategy

Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 0). The data extraction form will be piloted on 5 studies and modified as required before use. Information extracted will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

5.4 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed independently by two reviewers. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The study quality will be assessed according to recommendations made by the NHS Centre for Reviews and Dissemination[15] and the *Cochrane Handbook for Systematic Reviews of Interventions*.[16] This will include assessment of the following factors:

- random sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other bias.

5.5 Methods of analysis/synthesis

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, standard pair-wise meta-analysis will be performed to evaluate the clinical effectiveness. Treatment effects will be presented as relative risk for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Meta-analysis will be carried out using Comprehensive Meta Analysis software, with the use of fixed- and/or random-effects model appropriate to the assembled datasets. Statistical heterogeneity between included studies will be assessed by I^2 test. In the presence of heterogeneity ($I^2 > 30\%$) possible sources will be investigated, including differences between individual studies' populations, methods or interventions. Where feasible, the possibility of publication bias and/or small study effects will be investigated using funnel plots and Egger's tests.

6 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST-EFFECTIVENESS

A purpose of this MTA will be to assess the cost-effectiveness of permanent implantable dual-chamber pacemakers for patients with symptomatic bradycardia due to sick sinus syndrome without atrioventricular block in the UK. This objective will be met through identification and appraisal of:

- published economic evaluations from the literature or submitted economic evaluations from manufacturers' submissions (MSs);
- HRQoL studies of people with bradycardia;
- UK-specific resource use data: non-UK sources will be considered if there is insufficient UK-specific information;
- UK-specific cost data.

Should the published or submitted economic evaluations prove insufficient to answer the review question an independent *de novo* economic model will be developed.

6.1 Search strategy

The cost-effectiveness search will aim to identify full economic evaluations, costing studies and health state utility value (HSUV) studies. The following electronic databases will be searched in order to identify studies relevant to the scope of this MTA:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- NHS Economic Evaluations Database (NHS EED);
- HTA (Cochrane Library).

The details of the search strategy are presented in full in Appendix 9.1. The search strategy used will combine terms capturing the population (pacing), and interventions (dual) or comparators (single). The search terms used to capture evidence associated with comparators will be broader than those used in the search for clinical effectiveness evidence; i.e., including single-chamber ventricular as well as atrial pacing. This is because economic evaluations and HSUV studies in a patients receiving single chamber ventricular pacing are likely to be informative with respect to the scope of this MTA.

Health economic and quality of life search terms will be applied separately to capture the study designs of interest (cost-effectiveness, cost and quality of life, HSUVs). No language or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and MSs will be searched for additional references. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

6.2 Inclusion and exclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

Inclusion criteria:

- all economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation);
- any setting (to be as inclusive as possible);
- intervention or comparators as per the scope of TA88;
- study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- full publications;
- quality of life studies in bradycardia;
- costing/resource use studies in cardiac pacing.

Exclusion criteria:

- abstracts with insufficient methodological details;
- systematic reviews.

6.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. Tables 3 and 4 show the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 5).

Table 3. Health economic evaluation data extraction table

Author, year, country	**Perspective, discounting & cost year**	**Model type**	**Patient population**	**Intervention/ comparator**	**Outcomes**	**Results ICER (per QALY gained) incl uncertainty**
Reviewer's comments:						
Abbreviations used in table: QALY, quality adjusted life year						

Table 4. Quality of life data extraction table

Author, year, country	**Sample size**	**Patient population**	**Instrument (Valuation)**	**Utility results**
Reviewer's comments:				
Abbreviations used in table:				

Table 5. Data exclusion table

Bibliographic reference	Reasons for exclusion
Abbreviations used in table:	

6.4 Quality assessment strategy

All published economic evaluations identified within the review and any economic evaluations submitted by manufacturers to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against NICE's reference checklist for economic evaluations[17] together with the Philips checklist[18] on mathematical models used in technology assessments (see Appendix 9.3). Each economic evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist.

6.5 Methods of analysis

Published and submitted economic evaluations

A narrative summary and accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations.

Economic modelling

Should the economic evidence identified prove insufficient to answer the review question, a *de novo* economic model will be developed. The structure of the model will be informed by economic evaluations identified in the published literature and MSs; all structural assumptions will be documented and accompanying rationales provided. It is anticipated that the model used in TA88 to inform the cost-effectiveness of interventions in people with SSS without AV block will be the most informative in the development of the economic evaluation.[1] The clinical effectiveness parameters required for the economic model will be informed by the review of the clinical effectiveness literature outlined in Section 5. In addition, parameters such as estimates of quality of life (utility data) will be informed by the published literature identified in the systematic review. In cases where parameters required to populate the model are not available from studies identified in the HRQoL literature review, expert clinical opinion will be used to identify utility data from similar indications that may be used as proxy utility data.

The cost-effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per procedure avoided. As appropriate, cost data will be obtained from NHS reference costs,[19] British National Formulary,[20] Unit Costs of Health and Social Care,[21] published sources or MSs. Costs will

consist of direct medical costs (e.g. hardware costs and cost of adverse events, monitoring, and procedure costs) and direct non-medical costs (e.g. healthcare professional's costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.[17] The time horizon for the economic analysis will be lifetime in order to reflect the chronic nature of the condition.

6.6 Methods for estimating quality of life

Ideally, evidence of the impact of the treatments and condition that are the focus of this MTA on HRQoL will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related Technology Appraisals or clinical guidelines. In accordance with NICE methods guidance, where possible, utility values will be taken from studies that have been based on "public" preferences elicited using a choice-based method, preferably EQ-5D.[17] Mapping of HRQoL data to EQ-5D values will be considered on a case-by-case basis, using the University of Oxford Health Economics Research Centre's database of mapping studies.[22] Utility data will also be adjusted for age using data from the Health Survey of England.[23]

6.7 Analysis of uncertainty

As a standard, the model will be probabilistic; that is, all relevant input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the model's results. The outputs of probabilistic sensitivity analysis will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. In addition, uncertainty will also be explored through deterministic one-way sensitivity analysis. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity on cost-effectiveness results will be explored in subgroup analyses.

7 HANDLING THE COMPANY SUBMISSION(S)

All data submitted by the drug manufacturers/sponsors will be considered if received by the TAR group on or before 24/03/2014. Data arriving after this date will not be considered. Data meeting the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the manufacturer(s)'s submission(s), provided it complies with NICE's advice on

presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR group judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model.

Any 'commercial in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant manufacturer name, for example, in brackets). Any 'academic in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be highlighted in yellow and underlined in the assessment report.

8 COMPETING INTERESTS OF AUTHORS

None.

9 APPENDICES

9.1 Draft search strategies

9.1.1 Clinical draft search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; search run: 08/11/13

1 exp Pacemaker, Artificial/ (22,694)
2 exp Cardiac Pacing, Artificial/ (20,359)
3 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab (55,129)
4 or/1-3 (68,063)
5 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (2,111)
6 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (243)
7 ((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (805)
8 ((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (319)
9 (dual adj2 chamber).mp. (2,641)
10 (dual adj2 pac$).mp. (1,685)
11 double adj2 chamber.mp. (457)
12 physiologic$ adj2 pac$.mp. (441)
13 (AV adj2 synchron$).mp. (230)
14 (atrioventricular adj2 synchron$).mp. (245)
15 (AV adj2 sequential).mp (185)
16 (atrioventricular adj2 sequential).mp. (209)
17 DDD.mp. (4,467)
18 DDDR.mp. (390)
19 DDI.mp. (1,961)
20 DDIR.mp. (34)
21 VDD.mp. (591)
22 VDDR.mp. (74)
23 VDI.mp. (210)
24 VDIR.mp. (9)
25 or/5-24 (11,041)
26 (single adj2 chamber).mp. (1,048)
27 (single adj2 pac$).mp. (1,121)
28 (atrial adj2 pac$).mp. (5,937)
29 AAI.mp. (1,076)
30 AAIR.mp. (154)
31 or/26-30 (8,812)
32 Randomized Controlled Trials as Topic/ (102,421)
33 randomized controlled trial/ (389,900)
34 Random Allocation/ (81,721)
35 Double Blind Method/ (131,759)
36 Single Blind Method/ (19,575)
37 clinical trial/ (504,879)
38 clinical trial, phase i.pt. (16,184)
39 clinical trial, phase ii.pt. (26,878)
40 clinical trial, phase iii.pt. (10,160)
41 clinical trial, phase iv.pt. (997)

42 controlled clinical trial.pt. (89,890)
43 randomized controlled trial.pt. (389,900)
44 multicenter study.pt. (182,437)
45 clinical trial.pt. (504,879)
46 exp Clinical Trials as topic/ (296,147)
47 (clinical adj trial$).tw. (226,042)
48 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (134,662)
49 PLACEBOS/ (33,767)
50 placebo$.tw. (168,864)
51 randomly allocated.tw. (17,198)
52 (allocated adj2 random$).tw. (19,789)
53 or/32-52 (1,225,091)
54 case report.tw. (203,026)
55 letter/ (831,138)
56 historical article/ (300,182)
57 or/54-56 (1,322,844)
58 53 not 57 (1,194,828)
59 4 and 25 and 31 and 58 (319)

9.1.2 Health economic draft search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; search run: 11/11/13

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14 (atrioventricular adj2 synchron$).mp. (245)
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29 AAI.mp. (1,076)
30 AAIR.mp. (154)
31 (ventricular adj2 pac$).mp. (5,698)
32 VVI.mp (1,182)
33 VVIR.mp (293)
34 or/26-33 (14,333)
35 Health Economics.mp (2,086)
36 Economic evaluation.mp (5,369)
37 exp Costs and Cost Analysis/ (41,994)
38 cost benefit analysis/ (61,466)
39 exp models economic/ (10,344)
40 exp fees/ (27,078)
41 exp budgets/ (12,013)
42 (economic adj2 burden).tw. (4,490)
43 (expenditure* not energy).tw. (18,822)
44 Cost Effectiveness Analysis.mp (5,823)
45 (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw. (22,034)
46 Cost Minimization Analysis.mp (373)
47 (cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw. (100,004)
48 (decision adj1 (tree* or analys* or model*)).tw. (8,981)
49 (econom* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw. (193,788)
50 ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw. (4,319)
51 Markov*.tw (14,659)
46 or/29-45 (398,127)
47 4 and 25 and 28 and 46 (57)

9.1.3 Quality of life draft search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; search run: 11/11/13

1 exp Pacemaker, Artificial/ (22,694)
2 exp Cardiac Pacing, Artificial/ (20,359)
3 (pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab (55,129)
4 or/1-3 (68,063)
5 ((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (2,111)
6 (physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (243)
7 ((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (805)
8 ((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab. (319)
9 (dual adj2 chamber).mp. (2,641)
10 (dual adj2 pac$).mp. (1,685)
11 double adj2 chamber.mp. (457)
12 physiologic$ adj2 pac$.mp. (441)

13 (AV adj2 synchron$).mp. (230)
14 (atrioventricular adj2 synchron$).mp. (245)
15 (AV adj2 sequential).mp (185)
16 (atrioventricular adj2 sequential).mp. (209)
17 DDD.mp. (4,467)
18 DDDR.mp. (390)
19 DDI.mp. (1,961)
20 DDIR.mp. (34)
21 VDD.mp. (591)
22 VDDR.mp. (74)
23 VDI.mp. (210)
24 VDIR.mp. (9)
25 or/5-24 (11,041)
26 (single adj2 chamber).mp. (1,048)
27 (single adj2 pac$).mp. (1,121)
28 (atrial adj2 pac$).mp. (5,937)
29 AAI.mp. (1,076)
30 AAIR.mp. (154)
31 (ventricular adj2 pac$).mp. (5,698)
32 VVI.mp (1,182)
33 VVIR.mp (293)
34 or/26-33 (14,333)
35 exp Quality of Life/ (120,074)
36 ((quality adj3 life) or life quality or QOL).ti,ab.(156,725)
37 (HRQL or HRQOL or HRQol).ti,ab. (10,098)
38 (value adj2 life).ti,ab. or exp Value of Life/ (5,950)
39 (life adj2 qualit$3).tw. (153,868)
40 (quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/ (10,659)
41 daly.ti,ab. (822)
42 (disabilit$3 adj2 life).ti,ab. (2,153)
43 exp Health Status Indicators/ (202,013)
44 (sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw. (16,728)
45 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1,442)
46 (sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw (444)
47 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw. (2,911)
48 (sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (23)
49 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw. (338)
50 (euroqol or euro qol or eq5d or eq 5d or eq-5d).tw. (4,178)
51 (hye or hyes or health$ year$ equivalent$).tw. (64)
52 hui$1.tw. (1,163)
53 (willing$ adj2 pay).tw. (2,914)
54 (willing$ adj2 accept).tw. (1,043)
55 standard gamble$.tw. (702)
56 (health adj3 (utilit$3 or value$2 or preference$2)).tw. (7,193)
57 (visual analog$3 scale or VAS).tw. (39,363)
58 patient preference$2.tw. (4,805)
59 (person$ trade-off or person$ trade off or PTO).ti,ab. (620)

60 (Contingent value or contingent valuation).ti,ab. (412)
61 discrete choice.ti,ab. (640)
62 health status.ti,ab. or exp Health Status/ (130,976)
63 ((quality adj3 wellbeing index) or QWB).ti,ab. (178)
64 (health utilities index or HUI).ti,ab. (1,095)
65 (time trade off or time tradeoff or TTO or time trade-off).ti,ab. (1,220)
66 (utility or utilities).ti,ab. (123,279)
67 disutil$.ti,ab. (234)
68 disability.tw. (88,573)
69 (wellbeing or well-being or well being or qwb).ti,ab. (45,361)
70 quality of well being.tw. (361)
71 quality of wellbeing.tw. (8)
72 or/29-65 (742,128)
73 4 and 25 and 28 and 66 (214)

9.2 Data extraction form clinical effectiveness studies

Study details		
Study identifier		
Trial location		
Trial sponsor		
Recruitment period		
Patient enrolment		
Trial design		
Inclusion criteria		
Exclusion criteria		
Outcomes reported		
Subgroups		
Stratification		
Ethnicity		
Diagnostic criteria		
Duration of follow up		
Definitions		
Treatment	**Intervention**	**Comparator**
Pacemaker		
Programming		
Randomised, n		
Withdrawals, n (%)		
Concomitant medications		
Average follow up		
Baseline patient	**Intervention, n (%)**	**Comparator, n (%)**

characteristics					
Age, years (range)					
Male gender					
Previous history of AF					
Previous stroke					
Outcome	**Risk of Bias**	**Low**	**Unclear**	**High**	**Comments**
	Random sequence generation				
	Allocation concealment				
Mortality	Blinding (who [participants, personnel], and method)				
Morbidity	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Exercise capacity	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Cognitive function	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Requirement of further surgery	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Adverse effects of treatment	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Health related quality of life	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Outcome	**Intervention**				**Control**
N randomised					

Mortality						
AEs						
Heart failure						
AF						
Stroke						
Reoperation						
TRAEs						
TR AF						
TR device replacement						
Outcome	**Intervention**			**Control**		
N randomised						
	mean	**95% CI**	N	**mean**	**95% CI**	N
Exercise capacity						
Cognitive function						
HRQoL						
Abbreviations used in table: TRAE treatment related adverse events						

9.3 Health economic evaluation study quality assessment

***NICE reference case*[17]**

Attribute	Reference case	Reviewer's comments
Decision problem	The scope developed by NICE	
Comparator(s)	Alternative therapies routinely used in the NHS	
Perspective costs	NHS and Personal Social Services	
Perspective benefits	All health effects on individuals	
Form of economic evaluation	Cost-utility analysis	
Time horizon	Sufficient to capture differences in costs and outcomes	
Synthesis of evidence on outcomes	Systematic review	
Outcome measure	QALYs	
Health states for QALY	Described using a standardised and validated instrument	
Benefit valuation	Time-trade off or standard gamble	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	
Sensitivity analysis	Probabilistic sensitivity analysis	
Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QALY, quality adjusted life year.		

Philips checklist ([18])

Dimension of quality	Reviewers comments
Structure	
S1 Statement of decision problem/objective	
S2 Statement of scope/perspective	
S3 Rationale for structure	
S4 Structural assumptions	
S5 Strategies/comparators	
S6 Model type	
S7 Time horizon	
S8 Disease states/pathways	
S9 Cycle length	
Data	
D1 Data identification	
D2 Premodel data analysis	
D2a Baseline data	
D2b Treatment effects	
D2c Costs	
D2d Quality of life weights (utilities)	
D3 Data incorporation	
D4 Assessment of uncertainty	
D4a Methodological	
D4b Structural	
D4c Heterogeneity	
D4d Parameter	
Consistency	
C1 Internal consistency	
C2 External consistency	
Abbreviations used in table:	

Additional information that is needed by NETSCC, HTA and NICE.
Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

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Please indicate to whom you wish all correspondence to be addressed

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Timetable/milestones

A Progress Report (to NETSCC, HTA who forward it to NICE within 24hr) will be submitted 31 March 2014

A draft Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted in 2014 (Date TBC)

The Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 2 July 2014

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