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Implantable device monitoring versus usual care for managing individuals with heart failure (Protocol)

Koo K, Ferguson C, Ling LH, Cleland JGF, Inglis SC

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Implantable device monitoring versus usual care for managing individuals with heart failure.
Cochrane Database of Systematic Reviews 2019, Issue 8. Art. No.: CD013401.
DOI: 10.1002/14651858.CD013401.

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[Intervention Protocol]

Implantable device monitoring versus usual care for managing individuals with heart failure

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Editorial group: Cochrane Heart Group.
Publication status and date: New, published in Issue 8, 2019.

Citation: Koo K, Ferguson C, Ling LH, Cleland JGF, Inglis SC. Implantable device monitoring versus usual care for managing individuals with heart failure. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No.: CD013401. DOI: 10.1002/14651858.CD013401.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of using implantable device monitoring as an additional management tool for individuals with heart failure, compared with usual care alone.

BACKGROUND

Heart failure (HF) is a chronic disease that impairs quality of life and is associated with high rates of hospitalisation (McMurray 2012). Global health expenditure on HF is estimated to exceed USD 108 billion per annum, and is projected to increase by more than double in the next decade (Cook 2014; Mozaffarian 2016). The economic burden of HF is largely driven by the high rehospitalisation rates (McHugh 2013; Kilgore 2017).

The European Society of Cardiology (ESC) guidelines offer a Class I recommendation for multidisciplinary care-management programmes to reduce the burden of hospitalisation and prolong survival in people with HF; they also give a Class IIb consideration for the use of implantable monitoring systems for symptomatic individuals with previous hospitalisations to reduce recurring HF-related hospitalisations (Ponikowski 2016). Management of patients with the guidance of medical implantable devices is not yet widely implemented by clinicians or advised with a strong recommendation by international guidelines (Atherton 2018; Ponikowski 2016; Yancy 2017). Implantable devices used for remote monitoring cannot be expected to improve clinical outcomes unless they trigger therapeutic interventions.

Implantable cardiac monitoring usually involves scheduled in-office visits ranging from every three to six months, with clinical decisions being made from retrospective data collected during the visit (Wilkoff 2008). New methods for remote monitoring allow for remote management by detecting signs of clinical events in between the scheduled office visits, which enables timely clinical decisions to be made based on live data. Telemonitoring refers to the use of sensors capable of transmitting data to monitor individuals at a distance (Meystre 2005). More sophisticated implantable devices are being designed, trialled and commissioned that use innovative technology to monitor the severity and the progression of HF in a timely manner. It is vital that the early stages of worsening HF are detected in order to prevent deterioration of the indi-

vidual's health through timely and appropriate intervention. The hypothetical benefit of telemonitoring using implantable devices is the ability to provide diagnostic data before a scheduled hospital visit, which translates into benefits for individuals and healthcare organisations (Klersy 2016).

There are conflicting results across studies showing the benefits of using implantable device monitoring. The efficacy of these secondary prevention methods need to be studied to demonstrate whether the theoretical benefits translate into clinical benefits in terms of reducing rehospitalisation rates and improving survival.

Description of the condition

Heart failure (HF) is a clinical syndrome caused by structural and functional abnormalities in the heart muscles, leading to the impairment of ventricular filling or the ability to eject blood into circulation (Inamdar 2016). HF is a debilitating condition with adverse effects on the body, and it is becoming more common in developed countries due to the ageing population and longer survival after the onset of cardiovascular disease (Townsend 2012). Although pharmacological and device therapy have lowered five-year mortality rates, hospitalisation rates have not changed significantly and remain at 24% at 30 days and 48% at 60 days (Desai 2012). HF is being addressed as the epidemic of the 21st century (Luscher 2015).

There are 26 million people living with HF worldwide (Savarese 2017). In the USA, the current prevalence of HF is 5.7 million and is expected to rise by 46% within 10 years (Lam 2011). HF is characterised by structural cardiac abnormalities or cardiac dysfunction which impairs the ventricular function and leads to increased intra-cardiac pressures or reduced cardiac output at rest or during stress (Metra 2017). The condition is associated with debilitating symptoms such as dyspnoea, chronic coughing and fatigue, which affect the individual's quality of life (McMurray 2012). Pulmonary congestion, as a result of elevated left atrial and left ventricular filling pressures, is a common physiological change leading up to HF-related hospitalisations (Yu 2005).

Acute heart failure (AHF) is a life-threatening event, indicating a transition to a more debilitating phase of HF. The individual experiences signs of deteriorating heart function and a sudden onset of worsening symptoms (Gheorghiade 2005). These common episodes comprise up to 5% of emergency admissions across the USA and Europe (Cowie 2015). AHF is associated with one-year mortality and hospitalisation rates of 23.6% and 36% respectively, and so poses a greater burden on healthcare than stable HF, which has one-year mortality and hospitalisation rates of 6.4% and 14.5% respectively (Nieminen 2006).

Description of the intervention

Monitoring the signs and symptoms of HF is vital for timely interventions and to prevent the condition from worsening. The early symptoms attributed to HF (such as fatigue and shortness of breath) are often unspecific; more obvious manifestations, such as ankle swelling and pulmonary congestion, occur during the later stages or remain absent (Stevenson 1989). Ambulatory daily weight monitoring has been used as an indication of fluid status and has been used to titrate pharmacological therapies accordingly (Goldberg 2003). However, daily weight monitoring has yielded inconsistent results in minimising rehospitalisation rates (Goldberg 2003; Zhang 2009).

Usual HF management, such as daily weight monitoring and natriuretic peptides, are prone to low sensitivity to predict the onset of clinical deterioration while the individual is in their asymptomatic state (Yancy 2017). Strategies would be more valuable if they were able to combine the established benefits of telemonitoring and anticipate severe episodes of decompensation and recognise the subclinical compensations through continuous observation.

Technology has developed to allow preclinical detection of physiological changes related to AHF. The development of implantable technology since the introduction of pacemakers has allowed various physiological changes to be measured using implantable devices (Nangalia 2010). Advanced algorithms and wireless technology allow remote monitoring outside the clinic, as well as continuous 24-hour monitoring, and alert the clinicians whenever a threshold level is triggered. Implantable cardiac diagnostic medical devices predict sudden deterioration of the individual's heart condition using a specific physiological parameter. Some of the most advanced invasive monitoring technology from Medtronic - such as the OptiVol^{TM} feature within an implantable cardioverter defibrillator or cardiac resynchronisation therapy device - are capable of detecting intrathoracic impedance changes over time to assess fluid congestion in individuals with HF (Wang 2007). St. Jude Medical's CardioMEMS^{TM} HF system is the only monitoring system approved by the Food and Drug Administration that detects pulmonary artery pressure changes using a small sensor that is easily implanted in the pulmonary artery via percutaneous right heart catheterisation (Abraham 2011). The two main techniques which are used to detect the onset of decompensations are impedance monitoring and multi-parametric monitoring (of heart rate variability, activity, respiratory rate, etc.).

How the intervention might work

Implantable devices, such as cardiac resynchronisation therapy devices and implantable cardioverter defibrillators, have the capacity to continuously monitor physiological changes such as congestion, blood pressure, heart rate variability or respiration rate. In essence, implantable devices allow individuals to be monitored remotely or telemonitored, which has been shown to have benefits in reducing the risk of all-cause mortality and hospitalisations using non-invasive methods (Inglis 2017). Likewise, implantable device monitor-

ing may offer similar benefits and provide an early warning of impending decompensations associated with AHF. Despite the frequency of usual in-office follow-up consultations, the periods between such appointments and in-office diagnoses account for the majority of time. Implantable devices offer snapshots of the physiological changes and yield higher sensitivity rates, compared with non-invasive techniques and monitoring tools which are prone to low specificity (Varma 2013). Some implantable devices, such as the CardioMEMS^{TM} pulmonary artery pressure monitoring device, offer continuous monitoring which allows for more careful surveillance of the changes (Abraham 2011).

Why it is important to do this review

More invasive and innovative methods are emerging to monitor changes in physiological parameters that may be early signs of clinical deterioration in people with HF. The European Society of Cardiology (ESC) recognises the different types of telemedicine and states that "each approach needs to be assessed on its individual merit" (Ponikowski 2016). Effective monitoring is vital to detect the early stages of these conditions and to prevent deterioration of the individual's health through timely and appropriate intervention. This is the next step in healthcare management and has the potential to improve survival of those individuals with HF and to reduce the burden of healthcare costs. With healthcare expenditure predicted to increase by 127% within the next 10 years in the USA alone, it is important to assess the implications to both the individual and to the healthcare system (Heidenreich 2011). The potential benefits of implantable device monitoring for people with HF include reducing hospitalisations and improving survival, however this method is not widely implemented by clinicians or recommended by international HF guidelines (Atherton 2018; Ponikowski 2016; Yancy 2017). New implantable devices are continually being developed which allow remote monitoring via various technologies, however there are conflicting reports of clinical benefits of these systems across individual clinical trials (Saxon 2010; van Veldhuisen 2011). Our review aims to address this uncertainty.

OBJECTIVES

To assess the effects of using implantable device monitoring as an additional management tool for individuals with heart failure, compared with usual care alone.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include parallel-group randomised controlled trials (RCTs), including cluster-RCTs, that compared the use of implantable devices as an additional ongoing monitoring tool with usual care to usual care alone. We will exclude cross-sectional, case-control or retrospective studies. We will include all publication types, but where a full peer-reviewed publication is not yet available, studies published as a brief conference abstract will only be included if we are able to obtain sufficient information from the abstract or the study authors regarding methodology and outcomes; otherwise we will list such studies as 'ongoing' or 'awaiting classification'. Terminated studies will only be included if there are sufficient data outlining the primary outcomes. For cross-over trials, we will only include outcomes measured prior to cross-over (where data are available).

Types of participants

We will include trials that enrolled adults (aged 18 years or over) with a diagnosis of HF, regardless of left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) classifications. The participants must have been randomised into either a usual-care group or an intervention group using an implantable device for HF monitoring. Those participants in the intervention group must have been monitored at a distance.

Types of interventions

We will only examine implantable medical devices designed specifically for monitoring symptoms in individuals diagnosed with HF. Non-implantable medical devices used for monitoring, and in-clinic methods, will not be included. The study must define the capability of, and physiologic parameters measured by, the device used in the intervention. The intervention's physiological measures must be constantly monitored. Trials focusing on advanced therapies for HF, such as heart transplant or left ventricular assisting devices, will be excluded.

The 'usual care' implemented in each study must be outlined clearly and be the same for both the intervention and control group in terms of frequency of consultation and management. Some devices have an alert system for the user, but for the purposes of this review the audibility of device and alert messages to the user will not be considered.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Number of participants with at least one HF-related hospitalisation or rehospitalisation.

Secondary outcomes

1. Accumulative length of all-cause hospital stay.
2. Health-related quality of life, measured using a validated tool such as the 36-Item Short Form Survey (SF-36) (Ware 1992) ; Assessment of Chronic Illness Care (ACIC) (Bonomi 2002); or Heart Failure Symptom Scale (HFSS) (Pozehl 2006).
3. Adverse events (including infection and device failure).
4. Cost and cost savings.
5. Individual satisfaction with the implantable device, measured using a percentage score.
6. Self-care, measured using validated tools such as the Self-Efficacy Scale (Sherer 1982), and Self-Management Screening (SeMaS) tool (Eikelenboom 2015).

Search methods for identification of studies

We will search from January 2003 and we will impose no restrictions on language of publication or publication status. As far as we are aware, the first RCT using an implantable monitor for HF was conducted in 2008, hence we will commence our search five years prior to this date (Bourge 2008).

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
2. MEDLINE (Ovid, from January 2003 onwards).
3. Embase (Ovid, from January 2003 onwards).
4. CINAHL (EbscoHost, from January 2003 onwards).
5. SCOPUS (from January 2003 onwards).
6. TROVE (from January 2003 onwards).
7. IEEE Explore (from January 2003 onwards).

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) for ongoing or unpublished trials. We also search the Food and Drug Administration (FDA) https://www.fda.gov/MedicalDevices/.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies. We will scan the reference lists of all relevant primary studies and review articles for additional references.

We will also search the following websites of manufacturers for additional data from ongoing trials.

1. www.medtronic.com
2. www.abbott.com
3. www.biotronik.com
4. www.bostonscientific.com

Data collection and analysis

We will import all the identifiable abstracts and articles retrieved from the database searches into Covidence for referencing and screening (Covidence).

We will generate forest plots to demonstrate the effectiveness of implantable devices as an additional management tool compared to usual care alone.

Selection of studies

Two review authors (KK and CF) will independently screen the titles and abstracts of all the studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third review author will be asked to arbitrate (SCI or JGFC). We will retrieve the full-text study reports/publications and two review authors (KK and CF) will independently screen the full-text and identify studies for inclusion; they will also identify and record reasons for excluding the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (SCI or JGFC). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram, which will be produced in Covidence, and a 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (KK) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, date of study.
2. Participants: number (N), mean age, age range, gender, NYHA class, LVEF, recruitment status (i.e. recruited in hospital, after recent hospitalisation (e.g. within six weeks) or in stable HF), inclusion criteria and exclusion criteria, number of participants randomised, number of participants lost to follow-up and the number of participants analysed.

3. Interventions: implantable device measurement technology, variables measured and decision-support algorithms and comparison.
4. Outcomes: primary and secondary outcomes specified and collected, and time points recorded.
5. Study setting: country of study, number of study centres.
6. Devices: list of devices used.
7. Notes: funding sources, conflicts of interests, etc.

Two review authors (KK and CF) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (SCI or JGFC). One review author (KK) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (CF) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (KK and CF) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion or by involving another author (SCI or JGFC). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and will provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) with 95% confidence intervals. We will analyse continuous data as mean difference (MD) with 95% confidence intervals, if the studies use the same measurement tool for the outcome. If studies measure the same outcome with different tools (for example, quality of life), we will consider using standardised mean difference (SMD) to pool the studies. We will enter data presented as a scale with a consistent direction of effect.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

We do not anticipate any unit of analysis issues with the studies we plan to include. If we identify any non-standard designs (e.g. crossover or cluster-randomised trials) we will use recommendations from the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2017). For multiple-armed studies that compare more than one device with usual care, we will combine the device arms to have a single comparator against usual care. For studies reporting different lengths of follow-up we will use the longest follow-up from each study.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where possible, we will use the Review Manager 5 calculator to calculate missing standard deviations using other data from the trial, such as confidence intervals. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies. We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity (i.e. and I^2 value greater than 50%) we will report it and explore possible causes using prespecified subgroup analyses.

Assessment of reporting biases

If we are able to include 10 trials or more, we will create and examine funnel plots to explore possible study biases.

Data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will use a random-effects model as we expect some heterogeneity within the interventions.

If results for any outcome are significant, it will be expressed as Number Needed to Treat (NNT) to prevent one death, and NNT to prevent one HF-related hospitalisation.

'Summary of findings' table

We will create a 'Summary of findings' table using the two primary outcomes (all-cause mortality, HF-related hospital admissions and readmissions) and five of the secondary outcomes (accumulative length of all-cause hospital stay, health-related quality of life, adverse events, cost and cost savings, individual satisfaction). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use the methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), and will create the tables using GRADEpro GDT software (GRADEpro GDT 2015). By treating all implantable devices as one comparator, we will pool the data from the studies comparing implantable devices to usual care into a single meta-analysis, and report these in one 'Summary of findings' table. We will document in the footnotes of the tables all decisions to downgrade the quality of studies and we will make comments to aid the reader's understanding of the review where necessary.

Judgements about the quality of the evidence will be made by two review authors (KK and CF*)* working independently, and disagreements will be resolved by discussion or involving a third author (SCI or JGFC). Judgements will be justified, documented and incorporated into reporting of results for each outcome.

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review. See Table 1 for a template 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

Depending on the number of studies included, we will consider conducting the following subgroup analyses, using outcomes with heterogeneity.

We propose to undertake a subgroup analysis according to the physiological parameters that the implanted device measures/monitors as its primary measure, such as:

1. pulmonary artery pressure;
2. right ventricular pressure;
3. left atrial pressure;
4. lung fluid accumulations.

We propose to undertake a subgroup analysis according to the type of comparator (usual care) used by the studies, such as:

1. in-clinic follow-ups;
2. structured telephone support;
3. HF management programmes.

Sensitivity analysis

To test whether key methodological factors or decisions have affected the main result, we plan to carry out a sensitivity analysis which excludes studies that are at high or unclear risk of bias for random sequence generation, allocation concealment, and incomplete data. Where missing data are thought to introduce serious bias, we will conduct a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

Reaching conclusions

We will base our conclusions only on findings from the meta-analysis or from data of the included studies of this review (or both). We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline remaining uncertainties in the area.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Summary of findings table - draft

[*Intervention vs. control for the treatment of….]*

Patient or population:
Setting: [***e.g.*** *hospital, community*]
Intervention:
Comparison:

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with *control*	Risk with *treatment*				
All-cause mortality						
Number of participants with at least one HF-related (re)hospitalisation						
Accumulative length of all-cause hospital stay						

Table 1. Summary of findings table - draft (*Continued*)

Health-related quality of life						
Adverse events						
Cost and cost savings						
Individual satisfaction						

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 exp Heart Failure/ (111609)
2 ((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw. (169119)
3 1 or 2 (199624)
4 exp Telemedicine/ (24324)
5 exp Telecommunications/ (83611)
6 exp Telemetry/ (12265)
7 Monitoring, Physiologic/ (52338)
8 tele med*.tw. (117)
9 telecare*.tw. (606)
10 telecardiol*.tw. (185)
11 telemonitor*.tw. (1286)
12 tele-monitor*.tw. (122)
13 teleconsult*.tw. (1046)
14 teleconferenc*.tw. (1009)
15 telecommunicat*.tw. (3887)

16 telephon*.tw. (55445)
17 telehealth*.tw. (3272)
18 telemetry.tw. (6230)
19 (remote* adj3 consult*).tw. (411)
20 tele-consult*.tw. (74)
21 tele-conferenc*.tw. (17)
22 tele-health*.tw. (104)
23 Monitoring, Ambulatory/ (7637)
24 telehome.tw. (23)
25 tele-home.tw. (22)
26 phone*.tw. (31919)
27 telefon*.tw. (201)
28 telemed*.tw. (9310)
29 ehealth.tw. (1977)
30 e-health.tw. (1850)
31 mobile health.tw. (2328)
32 mhealth.tw. (2045)
33 m-health.tw. (300)
34 ((remote* or distan*) adj2 (care or caring or monitor* or program* or help or support*)).tw. (4916)
35 bluetooth.tw. (845)
36 (impedance adj2 monitor*).tw. (1014)
37 or/4-36 (224340)
38 invasiv*.tw. (338631)
39 internal*.tw. (446305)
40 implant*.tw. (368123)
41 Pacemaker, Artificial/ (25044)
42 Defibrillators, Implantable/ (15071)
43 or/38-42 (1142028)
44 randomized controlled trial.pt. (476544)
45 controlled clinical trial.pt. (92921)
46 randomized.ab. (435206)
47 placebo.ab. (195567)
48 drug therapy.fs. (2085204)
49 randomly.ab. (305887)
50 trial.ab. (454605)
51 groups.ab. (1883090)
52 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 (4381429)
53 exp animals/ not humans.sh. (4549808)
54 52 not 53 (3788748)
55 3 and 37 and 43 and 54 (226)
56 limit 55 to yr="2003 -Current" (200)

CONTRIBUTIONS OF AUTHORS

KK contributed to the design of the protocol, and was responsible for co-ordinating and completing the protocol, including writing the protocol.

CF contributed to the design of the protocol and writing of the protocol.

JGFC provided expert review of the protocol and contributed to the writing of the protocol.

HL provided expert review of the protocol and contributed to the writing of the protocol.

SCI was responsible for the conception and design of the protocol, and contributed to the writing of the protocol.

DECLARATIONS OF INTEREST

KK: none known.

SCI: none known.

CF: Dr Caleb Ferguson is supported by a 2018 Postdoctoral Research Fellowship (Ref:102168) from the National Heart Foundation of Australia. He has received funding from the Stroke Foundation, Australian College of Nursing, University of Technology, Western Sydney University and teaching honoraria from Pfizer. He is affiliated with Western Sydney University, Western Sydney Local Health District, University of Technology Sydney, Translational Health Research Institute (THRI) and Ingham Institute. He is Managing Editor of Contemporary Nurse and Associate Editor of BMC Cardiovascular Disorders. He is an executive member of the Cardiovascular Nursing Council of the Cardiac Society of Australia & New Zealand, a Board Director of the Australasian Cardiovascular Nursing College, Research Advisory Committee Member and Ambassador of the Stroke Foundation. He contributed to the authorship of the Heart Foundation Atrial Fibrillation Guidelines (2018) and Stroke Foundation Clinical Guidelines (2017).

HL: none known.

JGFC: Professor Cleland has received support for medical research from many companies manufacturing pharmaceuticals and devices for the management of heart failure and has received honoraria for lectures and advisory boards. Of greatest relevance to this review is the research support from Medtronic.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.
- NSW Cardiovascular Research Network, supported by the Heart Foundation and the NSW Office for Science and Medical Research, Australia.

Cardiovascular Life Sciences Fellowship to A/Prof Sally Inglis (2013-2017)

- Dr Caleb Ferguson is supported by a 2018 Postdoctoral Research Fellowship (Ref:102168) from the National Heart Foundation of Australia, Australia.
- Australian Government Research Training Scholarship, Australia.

To Kevin Koo