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Mechanical assist devices for acute cardiogenic shock (Protocol)

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Mechanical assist devices for acute cardiogenic shock

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A B S T R A C T

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

The primary objective of this review is to assess whether mechanical assist devices improve survival in individuals with acute cardiogenic shock.

B A C K G R O U N D

Description of the condition

Acute cardiogenic shock (ACS) is a state of inadequate organ perfusion secondary to acute heart failure (Shekar 2016). Despite advances in the management of cardiogenic shock, it remains the leading cause of death in hospitalised patients, regardless of aetiologies (Chung 2012). The incidence of acute cardiogenic shock (ACS) has increased two-fold from approximately 55,123 in 2004 to 126,555 in 2014, according to the largest publicly available data in the USA. Furthermore, the prognosis of ACS remains poor, with only 48% of patients surviving from diagnosis to hospital discharge, despite higher rates of revascularisation and use of intra-aortic balloon pumps (Mandawat 2017).

Although ACS is a state of end organ failure, attributed to inadequate cardiac output secondary to univentricular or biventricular dysfunction, it also encompasses a multiorgan dysfunction syndrome, involving the entire circulatory system (Mandawat 2017). Clinically, ACS is a state of organ hypoperfusion secondary to acute cardiac failure (Shekar 2016). This is characterised by persistent hypotension (systolic blood pressure < 80 mmHg to 90 mmHg or mean arterial blood pressure 30 mmHg lower than baseline, for greater than 30 minutes) with reduction in cardiac index to < 1.8 L/min/m^2 without haemodynamic support or < 2.0 L/min/m^2 to 2.2 L/min/m^2 with support and elevated filling pressures (left ventricular end-diastolic pressure (LVEDP) > 18 mmHg or right ventricular end-diastolic pressure (RVEDP) > 10 mmHg to 15 mmHg), a pulmonary capillary wedge pressure > 15 mmHg in the setting of adequate or elevated filling pressure, as well as clinical features of hypoperfusion (cool extremities, decreased urine

output, or altered sensorium) (Mandawat 2017; Reynolds 2008; Rihal 2015).

Myocardial infarction with left ventricular failure is the most common cause of cardiogenic shock, and cardiogenic shock occurs in approximately 5% to 8% of patients hospitalised with ST elevation myocardial infarction (STEMI) and 2.5% of non-STEMI cases (Babaev 2005; Fox 2007; Hasdai 2000). When cardiogenic shock complicates an acute myocardial infarction, the reported mortality rate is between 85% to 90% (Goldberg 2001). Any cause of acute and severe left ventricular or right ventricular dysfunction can lead to cardiogenic shock. Acute myopericarditis, Takotsubo cardiomyopathy and peripartum cardiomyopathy can all lead to reversible ventricular dysfunction which have good long-term prognosis, but only if the patient can be supported through the acute phase of cardiac failure and cardiogenic shock (Emmert 2011; Howell 2016; Kato 1999; Omerovic 2016; Zalewska-Adamiec 2016).

Description of the intervention

For patients with refractory cardiogenic shock despite maximal vasopressors, inotropic support and intra-aortic balloon pump, mortality approaches 100% (Hochman 2001). Survival in these cases may be possible by providing complete circulatory support with a mechanical assist device (Hendry 1995; Hill 1986; Holman 1995).

Mechanical assist devices provide mechanical circulatory support (MCS) which has the ability to maintain vital organ perfusion, to unload the failing ventricle thus reduce intracardiac filling pressures which reduces pulmonary congestion, myocardial wall stress and myocardial oxygen consumption. Mechanical assist devices also have the ability to augment coronary perfusion by supporting the circulation during procedures which aim to treat the underlying cause of cardiogenic shock, such as revascularisation or ablation of ventricular arrhythmia (Friedel 1992; Rihal 2015). This can allow time for myocardial recovery (bridge to recovery) or allow time to come to a decision as to whether the patient is a candidate for a longer-term ventricular assist device (VAD) either as a bridge to heart transplantation or as a destination therapy with a long-term VAD (Copeland 2004).

How the intervention might work

Current devices can be divided into categories: short-term versus long-term devices; paracorporeal versus intracorporeal; pulsatile versus continuous flow devices; full versus partial support devices; percutaneous versus surgical; and assist devices versus complete heart replacement (total artificial heart) (Sellke 2010).

In patients presenting with critical circulatory instability, the chosen mechanical assistance should be rapidly available and easily implantable. Standard cardiopulmonary bypass is designed to ensure minutes to hours of support for patients undergoing cardiac surgery. Extra corporeal membrane oxygenation (ECMO) provides continuous flow support to patients with respiratory, cardiac or combined cardiopulmonary failure for days to weeks. Deoxygenated blood is drained from the venous system, the pulmonary system is bypassed by placing an oxygenator in parallel with the native lungs and pumped in a continuous manner using a centrifugal or roller pump back to the arterial circulation (Bartkett 2010). Cannulation can be obtained centrally (blood being drained directly from the right atrium and returned to the proximal ascending aorta) or peripherally (blood draining from the proximal femoral or jugular vein and returned to the carotid axillary or femoral artery), typically using the Seldinger technique, via an open or percutaneous approach (Chamogeorgakis 2013). Venoarterial ECMO is available for cardiac or cardiopulmonary failure as a bridge to recovery, a bridge to definitive VAD, or bridge to heart transplantation (Squires 2016).

Similarly short-term VADs can be rapidly implantable and provide extracorporeal or paracorporeal pulsatile or continuous flow. VADs support the function of the left ventricle (left ventricular assist device (LVAD)), right ventricle (right ventricular assist device (RVAD)) or both ventricles (biventricular assist device (BiVAD)) depending on what is required for that particular patient. They do not include an oxygenator, thus providing isolated cardiac support. These devices are more expensive but allow the patients longer duration of circulatory support and greater opportunity to mobilise (Rihal 2015).

Pagani 1999 described a group of patients with refractory cardiogenic shock, treated with mechanical assistance with the intention to bridge to transplantation. Those with cardiac arrest or severe haemodynamic instability with evidence of multiorgan failure were initially placed on ECMO (N = 14) and the remaining with less severe status (N = 18) were immediately implanted with LVADs. Of those on ECMO, a total of seven (50%) eventually received LVADs, and one was directly transplanted. Ultimately, five of the ECMO to LVAD patients were transplanted and all of those transplanted survived to hospital discharge. Of the patients surviving ECMO to LVAD or ECMO to transplant, one-year survival (71%) was no different to the group directly implanted with LVADs (75%). These results suggest that ECMO resuscitation is an effective, resource sensitive strategy to salvage patients in extremis rather than the immediate implantation of a LVAD, which can instead be offered following a period of ECMO support, with no impact on subsequent survival (Pagani 1999).

Why it is important to do this review

The leading cause of death internationally is cardiovascular disease, and cardiogenic shock is the penultimate point in which there is an opportunity to intervene (Lü 2016).

Cardiac surgeons are faced with increasingly complex cases with significant co-morbidities, and with quality indexes, such as failure to rescue those who develop complications (e.g. postcardiotomy

cardiogenic shock) being increasingly assessed. In order to operate on such complex cases, having the knowledge of the best current evidence will provide hospital trusts with the essential information in providing the necessary equipment and in training staff in the use of mechanical support devices.

The National Institute for Clinical Excellence (NICE) guidelines: *Acute Heart Failure: diagnosis and management*, state that "at an early stage, the specialist should have a discussion with a centre providing MCS about people with potentially reversible severe acute heart failure or people who are potential candidates for heart transplantation" (NICE 2014).

The 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure include MCS as a treatment option for patients who cannot be stabilised on medical treatment alone. In addition to the uses described above, MCS, particularly ECMO, can be used as a 'bridge to decision' in patients with cardiogenic shock to achieve haemodynamic stability, to allow consideration of long-term MCS and heart transplant to be evaluated (Ponikowski 2016).

Many cardiology/cardiothoracic centres do not have timely access to temporary mechanical support devices. This review aims to assess the effectiveness of this treatment which would be valuable in guiding patient management and service planning.

OBJECTIVES

The primary objective of this review is to assess whether mechanical assist devices improve survival in individuals with acute cardiogenic shock.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing mechanical assist devices with best current intensive care management, including intra-aortic balloon pump and inotropic support. We will include studies reported as full-text, those published as abstract only, and unpublished data. We will not include crossover trials as we are looking at survival data in the setting of patients with an exceedingly high mortality risk.

Types of participants

We will include all participants, irrespective of age (adults and children), with a diagnosis of acute cardiogenic shock secondary

to any cause. Acute cardiogenic shock is defined as "a state of organ hypoperfusion secondary to acute cardiac failure" (Shekar 2016). This is characterised by persistent hypotension (systolic blood pressure < 80 mmHg to 90 mmHg or mean arterial blood pressure 30 mmHg lower than baseline, for greater than 30 minutes) with reduction in cardiac index to < 1.8 $L/min/m^2$ without haemodynamic support or < 2.2 $L/min/m^2$ with support and a pulmonary capillary wedge pressure > 15 mmHg in the setting of adequate or elevated filling pressure (Reynolds 2008; Rihal 2015). We will include studies with a subset of eligible participants in the review. If more than one of the included trials were found to have less than 75% of patients with the diagnosis of interest we would accept that this reduces the validity of the results; we would accept this and describe it as a limitation of the review.

Types of interventions

The intervention group is any participant treated with a mechanical assist device, including extra corporeal membrane oxygenation (ECMO), left ventricular assist device (LVAD), right ventricular assist device (RVAD), or biventricular assist device (BiVAD), compared to the control group which is the group treated with best current intensive care management, including inotropic support and intra-aortic balloon pump.

Types of outcome measures

The reporting of outcomes is not a criteria for inclusion in the review.

Primary outcomes

1. Survival (measured to: discharge; 30 days; 6 months; 1 year; end of follow-up)
2. Survival (measured to: transplant; unsupported cardiac function; end of follow-up)

Secondary outcomes

1. Quality of life (using a validated quality of life scale or questionnaire, measured to: discharge; 30 days; 6 months; 1 year; end of follow-up)
2. Major adverse cardiovascular events (measured to: discharge; 30 days; 6 months; 1 year; end of follow-up)
   i) cerebrovascular accidents (persistent central neurological deficit for greater than 72 hours)
   ii) myocardial infarction
   iii) acute limb ischaemia
3. Dialysis-dependent (measured to: discharge; 30 days; 6 months; 1 year; end of follow-up)
4. Length of hospital stay and length of intensive care unit stay

5. Major adverse events, for example, deep sternal wound infection, prolonged ventilation >72 hours (measured to: discharge; 30 days; 6 months; 1 year; end of follow-up)

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases.
- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (Ovid)
- Embase (Ovid)
- Web of Science Core Collection (Thomson Reuters)

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

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), the UK Clinical Research Network Portfolio Database (public.ukcrn.org.uk), and Centerwatch (www.centerwatch.com).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication. We will search relevant manufacturers' websites for trial information. (Manufacturers of mechanical assist devices that we have identified in previous searches: www.thoratec.com, www.maquet.com, www.medtronic.com, www.livanova.sorin.com, www.sjmglobal.com, www.hemoventgmbh.com, www.abiomed.com, www.reliantheart.com, www.novacor.co.uk, www.mylvad.com, www.jarvikheart.com, www.terumoheart.net, www.sunshineheart.com, www.heartware.com).

Searching other resources

We will check reference lists of all included studies and review articles for additional references. We will contact trial authors for missing data and through peer groups, identify any other ongoing trials. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Two teams of two review authors (JS, TN and CC, PA) will independently screen titles and abstracts for inclusion of all the potential 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 fifth review author will be asked to arbitrate (KB). We will retrieve the full-text study reports/ publications and two review authors (TN, JS) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (KB). 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 and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for extraction of study characteristics and outcome data which has been piloted on at least one study in the review. We will include studies irrespective of whether measured outcome data are reported in a usable way.

Two review authors (CC and JS) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, and date of study.

2. Participants: number of participants randomised to the intervention, number of participants lost to follow-up, number of participants analysed, mean age, age range, gender, cause of cardiogenic shock, diagnostic criteria, baseline lung function, smoking history, lactate prior to initiating mechanical circulatory support (MCS).

3. Interventions: type of mechanical assist devices, duration from diagnosis to intervention, duration of treatment, comparison, concomitant medications.

4. Outcomes: primary and secondary outcomes specified and collected, time points reported, number lost to follow-up and reasons for loss to follow-up.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (CC and JS) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third review author (PA). One review author (TN) will transfer data into the Review Manager 5 (RevMan 5) file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the review with the study reports. A second review author (JS)

will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (TNH and JS) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (PA). 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 assess selective outcome reporting bias by comparing the outcomes reported with the outcomes planned based on clinical trial registries/published protocols.

We will grade each potential source of bias as high, low or unclear and 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 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 review.

Measures of treatment effect

It is our intention to conduct the meta-analysis using the most informative outcome and matching methods. Given that our primary outcome is patient survival this would (ideally) involve the use of individual participant data (IPD) and the tools of survival analysis. We shall therefore contact the authors of studies identified in the review to request this data. If such data are available for a sufficient number of studies, we would perform the meta-analysis using Cox Regression with mixed effects, following the recommendations of a review of methods (Austin 2017). However, we accept that we may be unable to obtain IPD in all cases, and it may be necessary to resort to the use of aggregate data. In the case we are required to use aggregate data, we will opt for binary survival at discharge, 30 days, six months, and one year. We would

then conduct analysis using Poisson Regression modes and report hazard ratios (HRs) (Simmons 2005).

In addition to the primary measures, we would collect and report on outcomes such as overall survival, survival to transplant, survival to unsupported cardiac function and major adverse events. We will report confidence intervals of time to death and time to major adverse events, along with point estimates. We would describe dichotomous data relating to status at a fixed time point using risk ratios (RRs) with corresponding confidence interval (CI) (Higgins 2011). For continuous outcomes, we will calculate the mean difference (MD) between the treatment arms at the end of follow-up, if all trials measured the outcome on the same scale, otherwise we will pool standardised mean differences (SMDs).

Unit of analysis issues

Where studies report multiple observations for the same participant, we will include the data according to the closest time point where applicable (e.g. survival at 30 days and survival at 1 year). For quality of life data we will include the last follow-up time point collected and for adverse event data we will include the first event in meta-analyses and describe additional events for the same individual in the text.

In multiple-arm studies, where more than two interventional arms meet the eligibility criteria, we will combine the two device arms to have a single comparator (best current intensive care management, including intra-aortic balloon pump, and inotropic support).

As the intervention is in the setting of a life-threatening event, cross-over trials would not be possible, thus we do not anticipate cross-over trials.

In order to avoid unit of analysis errors in cluster-RCTs, we will conduct the analysis at the same level as the allocation, using a summary measurement from each cluster. Then the sample size is the number of clusters and analysis proceeds as if the trial was individually randomised (though the clusters become the individuals). However, this might considerably, and unnecessarily, reduce the power of the study, depending on the number and size of the clusters; we would acknowledge this as a limitation.

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 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 assess heterogeneity qualitatively by comparing the clinical and methodological characteristics of the included trials and by

visual inspection of forest plots to assess the degree of overlap in the CIs.

We will then compare heterogeneity quantitatively using the Chi^2 test of heterogeneity and the I^2 statistic in each analysis. We will consider a Chi^2 test resulting in P < 0.1 indicating significant statistical heterogeneity. We will interpret I^2 statistics in the following manner: 0% to 40%, potentially not important; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity (Deeks 2011).

If we find very high heterogeneity, we will first check the data specifically, questioning any outliers. If the data are correct, we will explore the results to understand why there is heterogeneity, and identify the factors that may be causing the variation between studies. If we find any modifiers, we will cautiously report the overall and subgroup analysis. We will note that the subgroup analysis is rarely randomised and we will caution that our results should be considered observational and hypothesis-generating, rather than definitive.

If we identify substantial or considerable heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

If the studies are too dissimilar in clinical (population, setting, intervention) and methodological heterogeneity (study design, risk of bias) and there is a high level of heterogeneity on visual inspection of the forest plots (I^2 > 90% and a Chi^2 with P < 0.1), then we would not proceed with meta-analysis (Higgins 2011).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and analyse a funnel plot to explore possible reporting biases for the primary outcomes.

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 for pooling of treatment effects, since the studies will differ in the mixes of participants and in the implementations of mechanical assist devices (Higgins 2011). We will present all results with the corresponding 95% CIs. We will conduct all analyses according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and with the statistical components of RevMan 5 software (Review Manager 2014).

If sufficient, clinically similar studies are available, we will pool the results in meta-analyses. For time-to-event data, we will pool HRs using the generic inverse variance facility of RevMan 5 (Review Manager 2014). For dichotomous outcomes, we will calculate the RR for each study and then pool. For continuous outcomes, we will pool the MDs between the treatment arms at the end of follow-

up if all trials measure the outcome on the same scale, otherwise we will pool SMDs.

We will descriptively summarise the studies for which pooling of results is not possible.

'Summary of findings' table

We will create a 'Summary of findings' table with the following outcomes and two time points.

Primary

1. Survival (30 days/end of follow-up)
2. Survival (to transplant or unsupported cardiac function/end of follow-up)

Secondary

1. Quality of life (using a validated quality of life scale or questionnaire; 30 days/end of follow-up)
2. Major adverse cardiovascular events (30 days/end of follow-up)
3. Dialysis-dependent (30 days/end of follow-up)
4. Length of hospital stay and length of intensive care unit stay
5. Major adverse events, for example deep sternal wound infection, prolonged ventilation (30 days/end of follow-up)

The comparison described in the 'Summary of findings' table will be mechanical assist devices with best current intensive care management, including intra-aortic balloon pump and inotropic support.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT software (GRADEpro GDT 2015). Two review authors (CC and JS) will assess the quality of evidence independently and decide on downgrading and upgrading. If no agreement can be reached, a third review author (PA) will resolve the discussion. We will justify all decisions to downgrade or upgrade the quality of the evidence using footnotes and we will provide comments to aid the reader's understanding of the review where necessary. We plan to only create one overall 'Summary of findings' table for our main analysis of mechanical assist devices with best current intensive care management (inotropic support and intra-aortic balloon pump).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Neonatal (less than 28 days of age)/paediatric (28 days to 16 years of age)/adult (greater than 16 years of age).

2. Cause of acute cardiogenic shock/ischaemic heart disease/cardiomyopathy/acute myopericarditis.

3. Mechanical assist device compared with intra-aortic balloon pump.

4. Mechanical assist device compared with best medical therapy excluding intra-aortic balloon pump.

5. Percutaneous mechanical assist devices (using Seldinger insertion technique) versus surgical mechanical assist devices (inserted via sternotomy/thoracotomy).

6. Long-term MCS devices (durable LVAD) compared with short-term MCS devices (for example, ECMO, Impella).

7. Compare patients who had refractory cardiac arrest with no cardiac arrest at the time of device implantation.

We will use the following outcomes in subgroup analyses.

1. Survival (to discharge/30 days/1 year/to end of follow-up)

2. Major adverse events (to discharge/30 days/1 year/to end of follow-up)

We will use the formal test for subgroup interactions in RevMan 5 (Review Manager 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Only including studies with a low risk of bias across all domains.

Brief economic commentary

We will develop a brief economic commentary based on current methods guidelines to summarise the availability and principal findings of trial-based and model-based economic evaluations (cost-analyses, cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) (Shemilt 2011; Shemilt 2017), that compare the use of mechanical assist devices to best current intensive care management, including intra-aortic balloon pump and inotropic support. We will identify relevant studies for this brief economic commentary during searches conducted for the review and during supplementary searches performed in accordance with search strategies developed by the Economics Methods Group (Shemilt 2017). This commentary will focus on the extent to which principal findings of eligible economic evaluations indicate that an intervention might be judged favourably (or unfavourably) from an economic perspective, when implemented in different settings.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline any remaining uncertainties in the area.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1. exp Heart Failure/
2. ((heart or cardiac or myocardial) adj2 fail*).tw.
3. Shock, Cardiogenic/
4. (Cardiogenic adj2 shock).tw.
5. 1 or 2 or 3 or 4
6. Heart-Assist Devices/
7. ((mechanical or heart) adj2 (assist or device*)).tw.
8. ((ventric* or biventric*) adj2 assist*).tw.
9. ((ventric* or biventric*) adj2 device*).tw.
10. (VAD or VADs or LVAD or LVADs or RVAD or RVADs or BIVAD or BIVADs).tw.
11. Extracorporeal Membrane Oxygenation/
12. ECMO.tw.
13. (extracorporeal adj3 membrane).tw.

14. (extracorporeal adj3 mechanical).tw.
15. (extracorporeal adj3 life support).tw.
16. ECLS.tw.
17. ELS.tw.
18. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 5 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. groups.ab.
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. exp animals/ not humans.sh.
29. 27 not 28
30. 19 and 29

Appendix 2. Glossary

Acute cardiac failure: sudden loss of heart function.

Acute myopericarditis: sudden inflammation of the heart muscle or the lining of the heart.

Cardiogenic shock: develops when the heart muscle has been damaged so extensively it can no longer pump enough blood to maintain the bodies function and if not reversed will lead to organ damage and death

Continuous flow: the pressure in the patients arterial system is continuous and does not change and the patient does not have a palpable pulse.

Haemodynamic support: medical help to maintain the blood supply to vital organs.

Heart failure: the heart is unable to effectively pump blood around the body

Intracorporeal ventricular assist device: is a pumping device which is situated inside the body that assists the heart to pump blood.

Left/right ventricular end diastolic pressure: the pressure in the left/right ventricle when the heart is at rest prior to contracting.

Myocardial infarction: heart attack.

Organ hypoperfusion: is a state where the organs are not receiving enough blood to receive adequate oxygen and nutrients to function/ stay alive.

Paracorporeal ventricular assist device: is a pumping device which is situated outside the body which is connected to the major blood vessels to assist the heart to pump blood.

Percutaneous device: is a device that is inserted via a needle through the skin into a blood vessel.

Peripartum cardiomyopathy: when a woman's heart muscle does not function well around the time of child birth.

Persistent hypotension: continuous low blood pressure.

Postcardiotomy cardiogenic shock: where a patients heart is able to pump after open heart surgery.

Pulsatile flow: blood flow which has a variable pressure and the patient has a pulse.

Refractory cardiogenic shock: the heart is no longer pumping adequately despite the maximum medical treatment.

ST elevation myocardial infarction: serious heart attack leading to heart muscle death.

Surgical device: is a device that is inserted via opening the body using a scalpel.

Takotsubo cardiomyopathy: broken heart syndrome, where the heart becomes suddenly weakened.

Univentricular/biventricular dysfunction: the heart has two pumping chambers, right and left ventricle. If one is not working properly this is univentricular dysfunction; if both are not working properly it is biventricular dysfunction.

Vasopressor/inotropic support: medications that increase blood pressure by helping the heart to pump stronger and faster.

CONTRIBUTIONS OF AUTHORS

TNH: wrote the first draft of the protocol and made amendments to revise the protocol as per editors comments

HB: reviewed all drafts of the protocol and reviewed and edited the revised protocol

KB: reviewed the first draft of the protocol

PA: reviewed and edited the revised protocol

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CC: reviewed the revised protocol

OB: reviewed and edited the revised protocol, adding statistical advice for the revised protocol

SW: reviewed the first draft of the protocol and reviewed the revised protocol

DECLARATIONS OF INTEREST

TNH: none known.

HB: none known.

KB: none known.

PA: none known.

JS: none known

CC: none known

OB: I have not received any payment (or benefits), either directly or indirectly, for my contribution to (or as a consequence of my involvement in) this project.

SW: Professor Westaby is medical director of Cell Therapy Ltd and founder and shareholder of Calon Cardiotechnology.

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