SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Animal models of heart transplantation from brain dead donors: A systematic review	
2.	Authors (names, affiliations, contributions)	Louise See Hoe[1], Matthew Wells[1,2], Johnny Millar[1], Aimee Khoo[3], Connie Boon[1], David McGiffin[4], John Fraser[1] [1]Critical Care Research Group, The Prince Charles Hospital, Brisbane Australia [2]Griffith University, Medical Sciences, Gold Coast, Australia [3]University of Queensland, Medical Sciences, St. Lucia, Australia [4] Cardiothoracic Surgery, The Alfred Hospital, Melbourne Australia	
3.	Other contributors (names, affiliations, contributions)	Nil	
4.	Contact person + e-mail address	Dr. Louise See Hoe (l.seehoe@uq.edu.au)	
5.	Funding sources/sponsors	Nil	
6.	Conflicts of interest	None declared.	
7.	Date and location of protocol registration	SYRCLE website	
8.	Registration number (if applicable)	N/A	
9.	Stage of review at time of registration	Planned	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Heart transplantation (Htx) is currently the only gold standard treatment for end stage heart failure and the greatest limitation to transplant (Tx) is the shortage of available donor hearts. Storage of donor hearts is restricted to a maximum of 4 hours in cold preservation solution on ice; thus, distance from donor to recipient is an important consideration when determining organ allocation. Numerous animal models of brain death (BD) for the intention of Tx have been used to investigate organ viability and for outcomes in the recipient post-tx. This review aims to investigate animal models of HTx, with a focus on BD induction and confirmation, storage means and medium and post-Tx outcome measures.	
	Research question		
11.	Specify the disease/health problem of interest	Heart transplantation from brain dead donors	
12.	Specify the population/species studied	All large and small animal models (excluding humans)	

13.	Specify the intervention/exposure	Induction of brain death	
14.	Specify the control population	Any, including - Healthy animals - Sham-injured controls	
15.	Specify the outcome measures	Any	
16.	State your research question (based on items 11-15)	What animal models of HTx from brain dead donors have been developed? Subquestions: - How has brain death been induced and confirmed in these animal models? How closely do these models replicate organ donor candidate conditions? - What storage techniques, solutions and time-frame have been utilised prior to transplantation? - How has the HTx been performed in animal models and what outcome measures are used to assess success of HTx? - What is the quality of the literature currently available describing these animal models and what are the existing knowledge gaps in the field of experimental HTx research?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed ☐Web of Science ☐SCOPUS X EMBASE XOther, namely: ☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	When available, please add a supplementary file containing your search strategy: [Brain Death Cardiac Transplantation Animal Models Search Strategy] Search strategy components identified in research question: - Cardiac transplantation - Brainstem death - Animal models Search strategy combined MeSH (PubMed) and Emtree (EMBASE) terms with possible free-text terms searched in title and abstract.	
19.	Identify other sources for study identification	X Reference lists of included studies ☐Books ☐Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	

20.	Define search strategy for these other sources	The reference lists of identified articles will be screened for potentially relevant titles not already retrieved by our search in PubMed and Embase and the full-text of these articles subsequently reviewed for inclusion.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	**After** removal of duplicates: **Phase I** – Screening of search results based on title and abstract only. **Phase II** – Full-text article evaluated for eligibility	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	(a) 2 reviewers will independently screen for relevant articles in both phases. (b) Articles between independent reviewers will be cross-matched and any discrepancies or disagreements will be resolved by discussion until consensus is reached or after collaboration with a third reviewer when no agreement is met (c) Studies deemed ineligible and their reasons for exclusion will be recorded in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	*Inclusion criteria:* All animal studies[[e.g. controlled studies and case series]]] *Exclusion criteria:*	
24.	Type of animals/population (*e.g.* age, gender, disease model)	*Inclusion criteria:* All non-human in vivo animal studies describing or using a model of brainstem death for HTx *Exclusion criteria:* - Ex-vivo studies and measurements - Not an animal experiment - In vitro models - Clinical (human) studies - Studies utilising animal models of donation after circulatory death as a single experimental group	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	*Inclusion criteria:* Studies involving: - Brain dead donors that progress to actual cardiac transplantation *Exclusion criteria:* - Studies involving multiorgan (including cardiopulmonary) Tx - Studies that did not proceed to Tx and solely examine ex-vivo or donor markers of cardiac function	
26.	Outcome measures	*Inclusion criteria:* - Any outcomes related to HTx *Exclusion criteria:* - None	

27.	Language restrictions	*Inclusion criteria:* - English language *Exclusion criteria:* - Non-English Language	
28.	Publication date restrictions	*Inclusion criteria:* - All years of publication *Exclusion criteria:* - No date restrictions on any searches	
29.	Other	*Inclusion criteria:* - Any *Exclusion criteria:* - Articles that are not an original or primary study: including reviews, editorials, comments, conference abstracts or lectures	
30.	Sort and prioritize your exclusion criteria per selection phase	**Selection phase 2** (screening title/abstract): 1. No original data 2. Not an in-vivo animal model 3. Not brainstem death or involving a heart from a non-brain dead donor only 4. No cardiac transplantation took place **Selection phase 3** (full text inclusion): As in selection phase 2 with addition of: 5. Abstract form only 6. Unretrievable in full text	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	- Author(s) - Year of publication - Study title - Journal published - Sponsorship - Country of publication	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	- Total number of animals - Intervention tested in the model (if applicable) - Number of experimental and control groups and number of animals per group - Study duration	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	- Animal species/strain and if genetically modified - Animal age, weight and gender - Presence of comorbid illnesses - Animal anaesthesia and analgesia - Animal airway interventions - Additional drugs/pre-treatments - Animal ventilation - Animal monitoring - Induction of brainstem death - Criteria for confirming brainstem death	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	- Time from confirming brain death to organ retrieval - Form and length of organ storage	

		- Ischaemic time: Time from donor heart retrieval to reperfusion - Method of cardiac transplantation - Additional co-intervention, study drugs or treatments - Recipient animal characteristics - Time spent recovering and monitoring post bypass weaning	
35.	Outcome measures	1. **Means of inducing and confirming brainstem death** Method to be compared against criteria outline by The Australian and New Zealand Intensive Care Society (ANZICS) Statement on Death and Organ Donation; Edition 3.1 2010 2. **Determining and measuring post-HTx organ viability and function** a. Successful weaning off cardiopulmonary bypass b. Biochemical and histological mechanistic analysis of blood and/or tissue c. Functional assessment including ECG and echocardiographic measures d. Imaging – as in MRI	
36.	Other (*e.g.* drop-outs)	- Mortality in animals (and cause of death) - Complications related to the technique of brainstem death induction or cardiac transplantation (if documented) - Number and reason for drop-outs	
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	a. 2 independent reviewers will assess risk of bias with the SYRCLE risk of bias tool and evaluate the study quality according to adherence with elements of the Animal Research: Reporting of In Vivo experiments (ARRIVE) Guidelines Checklist b. Discrepancies or disagreements will be resolved through discussion until consensus is reached or after collaboration with a third reviewer	
38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	By use of SYRCLE's Risk of Bias tool[4] X By use of SYRCLE's Risk of Bias tool, adapted as follows: - Experimental model well described in detail? Y/N - Reporting on temperature Y/N - Reporting on blinding/randomisation Y/N - Reporting of a power/sample size calculation Y/N ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other criteria, namely: As this is a review of animal models, no formal risk of bias will be completed. The study characteristics described in 32-36 will provide a general assessment of study quality and internal validity.	
	Collection of outcome data		

39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	The outcome measures listed in 35/36 are a range of qualitative and quantitative measures.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Data will be extracted to a computer-based data extraction form from text and tables, figures and author request for data that is not immediately available.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	(a) Data will be extracted by two independent reviewers (b) Discrepancies and disagreements will be resolved through discussion by the two reviewers or after collaboration with a third reviewer.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Included studies and their outcome parameters will be summarised descriptively.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A meta-analysis will be performed on functional measures of post-Tx data is the methods for each study from donor, storage and HTx do not differ greatly and is data is available.	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)		
45.	The statistical model of analysis (*e.g.* random or fixed effects model)		
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)		
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)		
48.	Any sensitivity analyses you propose to perform		
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)		
50.	The method for assessment of publication bias		
Final approval by (names, affiliations):		Date:	