SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Animal models of Acute Respiratory Distress Syndrome (ARDS) supported by Extracorporeal Membrane Oxygenation (ECMO): A systematic review	
2.	Authors (names, affiliations, contributions)	Jonathan E Millar[1], Nicole Bartnikowski[1], Nchafatso Obonyo[1], Matteo Di Nardo[2], Nathan Palpant[3], Danny F McAuley[4], John F Fraser[1] [1] Critical Care Research Group, University of Queensland, Brisbane, Australia [2] Paediatric Intensive Care Unit, Children's Hospital Bambino Gesù, Rome, Italy [3] Institute of Molecular Bioscience, University of Queensland, Australia [4] Centre for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom	
3.	Other contributors (names, affiliations, contributions)	Nil	
4.	Contact person + e-mail address	Dr Jonathan Millar (j.millar@doctors.org.uk)	
5.	Funding sources/sponsors	Nil	
6.	Conflicts of interest	None declared	
7.	Date and location of protocol registration	SYRCLE website – July 7th 2016	
8.	Registration number (if applicable)		
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?	Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a means of support for patients with acute severe respiratory failure which is unresponsive to conventional interventions, such as mechanical ventilation. Animal models have been important in the development and refinement of ECMO technology. The expansion of clinical ECMO necessitates a means of investigating novel therapeutic interventions in a relevant pre-clinical model. This review aims to describe the available animal models of ECMO and the Acute Respiratory Distress Syndrome (ARDS)/Acute lung injury (ALI).	
	Research question		
11.	Specify the disease/health problem of interest	Acute Respiratory Distress Syndrome (ARDS)	
12.	Specify the population/species studied	All animals (excluding humans)	

13.	Specify the intervention/exposure	Extracorporeal Membrane Oxygenation (ECMO)	
14.	Specify the control population	Any	
15.	Specify the outcome measures	Any	
16.	State your research question (based on items 11-15)	What models of ARDS/ALI, supported by contemporary ECMO, have been described? <u>Additionally</u> How has ARDS/ALI been defined in these models and what is its severity? How has ECMO been performed in animal models?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed X Web of Science ☐SCOPUS X EMBASE X Other, namely: Google Scholar ☐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: ECMO ARDS Animal Models SR Search Strategy	
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 included articles will be screened for relevant titles. The full text of any article identified by this means will be reviewed.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Phase I - Screening based on title/abstract Phase II - Screening of full-text articles	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	(a) 2 independent reviewers per phase (b) Discrepancies or disagreements will be resolved after discussion with a third reviewer	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: All original, full, non-human, in-vivo studies Exclusion criteria: - Ex-vivo studies or measurements - Review articles - Abstracts without a full description of methods - Articles citing the use of a relevant model which has been previously fully described and which does not include new information	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: All non-human animal studies describing (or a model of): - Acute Respiratory Distress Syndrome (ARDS)	

		- Acute Lung Injury (ALI) Exclusion criteria: - Clinical (human) studies - Studies with a disease model not representative of ARDS/ALI	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Studies involving: - Extracorporeal membrane oxygenation (veno-arterial or veno-venous) Exclusion criteria: Studies solely examining: - Extracorporeal Carbon Dioxide Removal - Cardiopulmonary Bypass - Intravascular Oxygenation Devices	
26.	Outcome measures	Inclusion criteria: Any Exclusion criteria: None	
27.	Language restrictions	Inclusion criteria: English Language Exclusion criteria: Non-English Language	
28.	Publication date restrictions	Inclusion criteria: 1st January 1996 - Current Exclusion criteria: Publication before 1st January 1996	
29.	Other	Inclusion criteria: NA Exclusion criteria: NA	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase I: 1. Not an animal model 2. Not ECMO 3. Not ARDS/ALI 4. Not an in-vivo study Selection phase II: 1. Not an animal model 2. Not ECMO 3. Not ARDS/ALI 4. Not an in-vivo study 4. Abstract form 6. Any article citing the use of a relevant model which has previously been fully described AND not including new information	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	- 1st Author - Year of publication - Title - Journal	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	- Total number of animals - Intervention tested in the model (if applicable) - Experimental groups (number of animals per group) - Study duration	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	- Animal species - Animal age, weight and sex - Animal anaesthesia and analgesia (pre-treatment, induction and maintenance of anaesthesia)	

		- Animal airway Interventions (endotracheal intubation versus tracheostomy) - Animal ventilation (means, mode and common parameters) - Animal monitoring - Additional study drugs or treatments - Study definition of ARDS/ALI in model - Means of inducing ARDS/ALI - Time from injury induction to achievement of injury criteria	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	- Mode of ECMO - ECMO cannulation strategy/configuration - ECMO flow rate - ECMO oxygenator/sweep gas parameters - Animal anticoagulation during ECMO - ECMO duration - Time from injury to commencement of ECMO	
35.	Outcome measures	- **Was ARDS/ALI achieved?** Using the definition and criteria set out in: *An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. Am J Respir Cell Mol Biol. 2011 May;44(5):725-38* - **Quantitative measurements of ARDS/ALI severity** Using the measures set out in: *An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. Am J Respir Cell Mol Biol. 2011 May;44(5):725-38* Broadly: (1) Measurements of Histological Evidence of Tissue Injury (2) Measurements of Alteration of the Alveolar Capillary Barrier (3) Measurements of the Inflammatory Response (4) Measurements of Physiological Dysfunction	
36.	Other (*e.g.* drop-outs)	- Mortality in animals (and cause of death) - Complications related to the technique of injury induction, ARDS/ALI or ECMO (if documented)	
	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 (b) Discrepancies or disagreements will be resolved after discussion 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] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows:	

		X Other criteria, namely: As this is a review of animal models no formal of risk of bias will be completed. The study characteristics described in 32-36 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 piloted data extraction form in the following steps: 1. Data extraction from text or tables 2. Data extraction from figures using a digital screen ruler 3. Data not available on review of articles will be requested from the study authors	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Two independent reviewers will extract data. Discrepancies or disagreements will be resolved after discussion 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)	Models will be summarised by descriptive means.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	As this is a review of models no meta-analysis will be performed.	
	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)	NA	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	NA	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	NA	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	NA	
48.	Any sensitivity analyses you propose to perform	NA	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	NA	
50.	The method for assessment of publication bias	NA	

Final approval by (names, affiliations):	Jonathan Millar	Date: