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 for studying potential cystic fibrosis treatments - A systematic review	
2.	Authors (names, affiliations, contributions)	CHC Leenaars RBM de Vries -student (s)- -clinician- FR Stafleu M Ritskes-Hoitinga	
3.	Other contributors (names, affiliations, contributions)	anonymous patient P Mercus C Punt T Ritsema W Beumer FLB Meijboom	
4.	Contact person + e-mail address	Cathalijn.Leenaars@radboudumc.nl	
5.	Funding sources/sponsors	NWO	
6.	Conflicts of interest	-	
7.	Date and location of protocol registration	Date: 23-DEC-2015 Location: SYRCLE website	
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?	For CF, a multitude of animal models is available to the researcher. Part of these models have been reviewed by several authors, focussing on e.g. genetic mouse models [Wilke et al, 2011] or on specific disease aspects [Olivier et al., 2015] but a complete systematic review is so far lacking. A complete and structured overview can help researchers working on CF to choose the most appropriate model for their question. The choice of the model will depend on the question; we intend to provide more specific advice for certain types of questions.	
	Research question		
11.	Specify the disease/health problem of interest	Cystic Fibrosis (CF)	
12.	Specify the population/species studied	All non-human animals	
13.	Specify the intervention/exposure	any (We define animal model for CF as animals in which a spontaneous or induced pathological process can be investigated, in which the process, according to the	

		authors, is intended to represent CF in humans in one or more respects.)	
14.	Specify the control population	-	
15.	Specify the outcome measures	any	
16.	State your research question (based on items 11-15)	What are the currently available animal models for CF (to perform e.g. a proof-of-principe / preclinical efficacy study for a new compound)? Subquestions: • What has been measured as a surrogate for CF? • Which aspects of the human disease have been modelled?	
	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 ☐ Other, 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])	Search strategy provided below.	
19.	Identify other sources for study identification	☐ Reference lists of included studies ☐ Books X Reference lists of relevant reviews ☐ Conference proceedings, namely: ☐ Contacting authors/ organisations, namely: ☐ Other, namely: Figshare / DOAJ?	
20.	Define search strategy for these other sources	All reviews will be screened full-text. When they mention models that are not otherwise included, we will retrieve the referred papers.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1. prescreening of title/abstracts 2. screening of full-text	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	2 for phase 1; discussion between reviewers 2 for phase 2; discussion between reviewers	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: • any full paper adressing cystic fibrosis in animals • any mutation / intervention inducing CF-like symptoms induced in live animals • Authors'intention to study CF Exclusion criteria: • Study not adressing cystic fibrosis • Study not in animals • Study describing ex-vivo measurements of tissue dissected from healthy animals • abstracts (without a full description of materials	

		and methods, e.g. conference procedings) • not a primary study / no new data	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: any animal Exclusion criteria: not an animal study	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: - Exclusion criteria: -	
26.	Outcome measures	Inclusion criteria: any Exclusion criteria:-	
27.	Language restrictions	Inclusion criteria: any Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: any Exclusion criteria: -	
29.	Other	Inclusion criteria:- Exclusion criteria:-	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase 1 (TI/AB): 1. No cystic fibrosis 2. No animal model for cystic fibrosis Selection phase 2 (full text): 1. CF not intent of study 2. No animal model 3. No primary study, or review not containing new data	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	• 1st author • year • title • journal • language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	• Number of animals • Control group • Laboratory temperature • Laboratory humidity • Laboratory lighting regime <u>Study quality indicators:</u> • statistical power • Randomisation (/latin-squaring /counterbalancing) • Blinding of experimenters & caretakers • groups using this model (more than 1 location)	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	• Animal • Strain • Line • supplier • Sex • Animal weight (start & end) • Animal temperature • Specific diet • administration of laxative / other co-medication • special bedding • Method of model induction (mutation / other) • Animal age at model induction (if not innate)	

		• Time & duration of model induction (for non-genetic models)	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	-	
35.	Outcome measures	All (qualitative)	
36.	Other (*e.g.* drop-outs)	% survival per group & cause of death Other drop-outs + reason	
	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	1 Please refer to point 38 and 41 for further information.	
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: Replace "random" by "random or appropriately blocked (Latin-Square)" ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: XOther criteria, namely: *Extracted study design characteristics (point 32) will be tabulated. This information (or lack of it) provides an indication of study quality, internal validity and risk of bias. As this is a model-focussed SR, no formal risk of bias will be done.*	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Qualitative extraction on the type of measurements (see 35)	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	-	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	A random sample of at least 5% of the included papers will be checked by an independent observer for accuracy of data-extraction.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	A descriptive overview of the various models will be given. Models will be clustered by induction method (mutation / other), species and strain.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	No meta-analysis will be performed	
	No meta-analysis will be performed.		
Final approval by (names, affiliations):		Dr. Cathalijn H.C. Leenaars, SYRCLE Dr. Rob BM. de Vries	Date: 23-DEC-12

References

de Vries RB, Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Updated version of the Embase search filter for animal studies. Lab Anim. 2014;48(1):88. doi: 10.1177/0023677213494374.

Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. Lab Anim. 2010 Jul;44(3):170-5. doi: 10.1258/la.2010.009117

Olivier AK, Gibson-Corley KN, Meyerholz DK. Animal models of gastrointestinal and liver diseases. Animal models of cystic fibrosis: gastrointestinal, pancreatic, and hepatobiliary disease and pathophysiology. Am J Physiol Gastrointest Liver Physiol. 2015 Mar 15;308(6):G459-71. doi: 10.1152/ajpgi.00146.2014.

Wilke M, Buijs-Offerman RM, Aarbiou J, Colledge WH, Sheppard DN, Touqui L, Bot A, Jorna H, de Jonge HR, Scholte BJ. Mouse models of cystic fibrosis: phenotypic analysis and research applications. J Cyst Fibros. 2011 Jun;10 Suppl 2:S152-71. doi: 10.1016/S1569-1993(11)60020-9.

Search strategy for PubMed

Cystic fibrosis [MeSH] OR Mice, Inbred CFTR [MeSH] OR Cystic Fibrosis Transmembrane Conductance Regulator [MeSH] OR

(cystic[tiab] AND (fibrosis[tiab] OR fibroses[tiab] OR fibrotic[tiab])) OR Mucoviscidos* [tiab] OR Mucoviscoid* [tiab] OR Mukoviszid* [tiab] OR CFTR [tiab] OR Fibrocystic Disease [tiab] OR Fibrocystic Diseases [tiab] OR Mckusick [tiab] OR CFRD [tiab] OR "pancreas cystic disease" [tiab] OR muco-patient* [tiab] OR muko-patient* [tiab] OR

(CF [tiab] AND (lung [tiab] OR lungs [tiab] OR pulmonary [tiab] OR ABPA [tiab] OR mucus [tiab] OR liver [tiab] OR livers [tiab] OR steatosis [tiab] OR cirrhosis [tiab] OR cirrhotic [tiab] OR meconeum ileus [tiab] OR gastrointestinal [tiab] OR intestine [tiab] OR intestines [tiab] OR intestinal [tiab] OR duodenum [tiab] OR jejunum [tiab] OR colon [tiab] OR caecum [tiab] OR DIOS [tiab] OR ((sweat [tiab] OR eccrine [tiab] OR apocrine [tiab] OR salivary [tiab] OR parotid [tiab] OR sublingual [tiab] OR submandibular [tiab] OR sub-lingual [tiab] OR sub-mandibular [tiab] OR von Ebner [tiab]) AND (gland [tiab] OR glands [tiab])) OR ((Paranasal [tiab] OR Para-nasal [tiab] OR frontal [tiab] OR ethmoidal [tiab] OR maxillary [tiab] OR sphenoidal [tiab]) AND (sinus [tiab] OR sinuses [tiab])) OR pancreas [tiab] OR pancreatic [tiab]))

AND the SYRCLE animal filter [Hooijmans et al., 2010]

Search strategy for Embase

Cystic fibrosis/ OR cystic fibrosis transmembrane conductance regulator/ OR (cystic adj2 fibros*).ti,ab,kw. OR fibrocystic diseas*.ti,ab,kw. OR (mucovisc* or Mukoviszidose).ti,ab,kw. OR CFRD.ti,ab,kw. OR muco-patient*.ti,ab,kw. OR muko-patient*.ti,ab,kw. OR

pancreas cystic disease.ti,ab,kw. OR pancreas fibrocystic disease.ti,ab,kw. OR pancreas fibrosis.ti,ab,kw. OR pancreatic cystic disease.ti,ab,kw. OR pancreatic fibrosis.ti,ab,kw. OR

(CF adj30 (lung OR liver OR stomach OR intestines OR pulmonary OR meconeum ileus OR gastrointestinal OR intestine OR intestines OR intestinal OR pancreas OR pancreatic OR ((sweat OR eccrine OR apocrine OR salivary OR parotid OR sublingual OR submandibular OR von Ebner) adj2 (gland OR glands)) OR ((Paranasal OR frontal OR ethmoidal OR maxillary OR sphenoidal) adj2 (sinus OR sinusses)))).ti,ab,kw.

AND the SYRCLE animal filter [de Vries et al., 2014]