**SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES**

**FORMAT BY SYRCLE (WWW.SYRCLE.NL)**

**VERSION 2.0 (DECEMBER 2014)**

<table>
<thead>
<tr>
<th>Item #</th>
<th>Section/Subsection/Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>A. General</td>
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<tr>
<td>1.</td>
<td>Title of the review</td>
<td>Animal models for studying potential cystic fibrosis treatments - A systematic review</td>
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</table>
| 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 | | |
| 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. |
<p>| 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 |</p>
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<td>14. Specify the control population</td>
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<td>15. Specify the outcome measures</td>
<td>any</td>
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| 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 | □ EMBASE |
| 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  
□ 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:  

| Type of study (design) | Inclusion criteria:  
- any full paper addressing cystic fibrosis in animals  
- any mutation / intervention inducing CF-like symptoms induced in live animals  
- Authors’ intention to study CF | Exclusion criteria:  
- Study not addressing cystic fibrosis  
- Study not in animals  
- Study describing ex-vivo measurements of tissue dissected from healthy animals  
- abstracts (without a full description of materials |
### Study characteristics to be extracted (for assessment of external validity, reporting quality)

| 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 |

| 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  

Study quality indicators:  
• 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) |
### Intervention characteristics (e.g. intervention, timing, duration)
- Time & duration of model induction (for non-genetic models)

### Outcome measures
- All (qualitative)

### 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

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<td>1</td>
<td>Please refer to point 38 and 41 for further information.</td>
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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
- 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.
- By use of CAMARADES' study quality checklist, adapted as follows:
  - Other 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.**

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**Final approval by (names, affiliations):**
- Dr. Cathalijn H.C. Leenaars, SYRCLE
- Dr. Rob BM. de Vries

**Date:** 23-DEC-12
References


Search strategy for PubMed


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 meconium 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]