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	The protective effect of anterior cruciate ligament reconstruction on articular cartilage: a systematic review of animal studies	
2.	Authors (names, affiliations, contributions)	Claudia Deckers, Radboudumc, Nijmegen, The Netherlands Gerjon Hannink, Orthopaedic research laboratory, Radboudumc, Nijmegen, The Netherlands Carlijn Hooijmans, SYRCLE, Radboudumc, Nijmegen, The Netherlands A. Tillema, information specialist Medical library Radboudumc	
3.	Other contributors (names, affiliations, contributions)	N.A	
4.	Contact person + e-mail address	Claudia Deckers Claudia.deckers@radboudumc.nl	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	19/07-2016	
8.	Registration number (if applicable)	N.A.	
9.	Stage of review at time of registration	Conducting the search	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Many studies have shown that ACL deficient knees will deteriorate radiologically and functionally over time due to advancing osteoarthritis. For this reason the anterior cruciate ligament is often reconstructed. However the protective benefit of ACL reconstruction in preventing cartilage damage has not been clearly established.	
	Research question		
11.	Specify the disease/health problem of interest	Anterior cruciate ligament injury	
12.	Specify the population/species studied	Animals	
13.	Specify the intervention/exposure	Anterior cruciate ligament reconstruction	
14.	Specify the control population	Intact and ruptured/transected ACL	
15.	Specify the outcome measures	Cartilage damage	
16.	State your research question (based on items 11-15)	Does anterior cruciate ligament reconstruction prevent cartilage damage?	

	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	√**MEDLINE via PubMed** ☐Web of Science ☐SCOPUS √**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])	When available, please add a supplementary file containing your search strategy: *searchstrategy 1*	
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:	
20.	Define search strategy for these other sources		
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Phase 1: Screening based on title and abstract Phase 2: Full text screening	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Number of reviewers: 2 Discrepancies will be solved by discussion	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: controlled interventional design (ACL transection as positive control and/or sham or non operated as negative control.) Exclusion criteria: non original studies	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: experimental animals Exclusion criteria: Humans, ex vivo, in vitro	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: ACL reconstruction Exclusion criteria: co interventions (biological mediators)	
26.	Outcome measures	Inclusion criteria: gross macroscopic assessment, histological/histochemical based grading, immunohistochemistry based grading, histomorphometry, biomechanical characterization, radiographic assessment, MRI Exclusion criteria: non relevant outcome measures	
27.	Language restrictions	Inclusion criteria: all languages Exclusion criteria:	
28.	Publication date restrictions	Inclusion criteria: Exclusion criteria: none	
29.	Other	Inclusion criteria: Exclusion criteria:	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: 1 1. not original studies 2. not animal studies	

		3. not ACL 4. not reconstruction Selection phase2: 5. not relevant outcome measure 6. no relevant control group 7. not isolated ACL	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, year, journal	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Experimental groups, number of animals included	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Species Age Gender	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of reconstruction Timing of reconstruction Time from reconstruction till cartilage inspection Time from ACL transection till cartilage inspection	
35.	Outcome measures	Cartilage damage	
36.	Other (*e.g.* 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	Number of reviewers: 2 Discrepancies will be solved by discussion	
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:** **In addition we will assess reporting of: any blinding, any randomization measures.** ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other criteria, namely:	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Gross macroscopic assessment of damage(Grading or determining the area of articular cartilage with gross morphological changes, ICRS scores, outerbridge scores, either with or without staining methods) Histological histochemical grading of changes in articular cartilage (Mankin grading method) Histomorphometrics (any kind of quantitative study on microscopic images of articular cartilage) Biomechanical characterization of articular cartilage (tensile and compressive measures of stiffness)	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using	If results are presented incomplete we will attempt to contact the author. If results are presented graphically	

	a digital screen ruler, then contacting authors)	only, data will be converted to numerical data using digital ruler software.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Number of reviewers: 2 Discrepancies will be solved by discussion	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Meta-analysis	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A meta-analysis will be performed whenever three of more independent comparisons per outcome category could be included. For the subgroup analysis a minimal of 3 studies per subgroup is required.	
	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)	If possible mean difference otherwise standardized mean difference	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	Random effects model	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Sex, type of reconstruction, species, timing	
48.	Any sensitivity analyses you propose to perform	Timing	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Correction of p-value for the number of subgroup analyses by Bonferroni-Holmes correction. Correction for multiple comparisons with the same control group by dividing the number of control animals by the number of comparisons with the control group.	
50.	The method for assessment of publication bias	For MD: produce funnel plots and analyse these plots for outcome measures with at least 15 studies. Funnel plot analysis will not be performed for SMDs because of the risk of funnel plot skewing.	
Final approval by (names, affiliations):		CR Hooijmans	Date: 20/07/2016