

## SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

ltem #	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	
	Other contributors (names,	Radboudume	
3.	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		1
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?	

## FORMAT BY SYRCLE (<u>WWW.SYRCLE.NL</u>) VERSION 2.0 (DECEMBER 2014)

Search and study identification           Identify literature databases to search (e.g. Pubmed, Embase, Web of science)         VMEDUINE via PubMed         Web of Science           17.         (e.g. Pubmed, Embase, Web of science)         Scopus         VemBase           18.         Define electronic search strategies (e.g. use the stee by step search sudder" and animal search filters <sup>10</sup> , 21, sudder" and animal search filters <sup>10</sup> , 21, sudder sudder" and animal search filters <sup>10</sup> , 21, sudder sudder" and animal search filters <sup>10</sup> , 21, sudder sudder sudde		C. Methods			
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28.       Publication date restrictions       Exclusion criteria: none         29.       Other       Inclusion criteria: Exclusion criteria: Exclusion criteria: Selection phase: 1	27.				
29.       Other       Inclusion criteria: Exclusion criteria: Exclusion criteria:         Sort and prioritize your exclusion       Selection phase: 1	28.	Publication date restrictions			
29.     Other     Exclusion criteria:       Sort and prioritize your exclusion     Selection phase: 1					
Sort and prioritize your exclusion Selection phase: 1	29.	Other			
I Nort and prioritize vour exclusion					
30. 1. not original studies	30.		1. not original studies		
criteria per selection phase 2. not animal studies		criteria per selection phase	-		

		3. not ACL	
		3. not ACL 4. not reconstruction	
		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	or assessment of external validity, reporting quality)	
31.	Study ID (e.g. authors, year)	Authors, year, journal	
	Study design characteristics (e.g.		
32.	experimental groups, number of	Experimental groups, number of animals included	
	animals)		
	Animal model characteristics (e.g.	Species	
33.	species, gender, disease induction)	Age	
	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Gender	
		Type of reconstruction	
24	Intervention characteristics (e.g.	Timing of reconstruction	
34.	intervention, timing, duration)	Time from reconstruction till cartilage inspection	
		Time from ACL transection till cartilage inspection	
35.	Outcome measures	Cartilage damage	
36.	Other ( <i>e.g.</i> drop-outs)		
	Assessment risk of bias (internal validity	/) or study quality	
	Specify (a) the number of reviewers		
27	assessing the risk of bias/study quality	Number of reviewers: 2	
37.	in each study and (b) how	Discrepancies will be solved by discussion	
	discrepancies will be resolved		
		□By use of <u>SYRCLE's Risk of Bias tool<sup>4</sup></u>	
		${f V}$ By use of SYRCLE's Risk of Bias tool, adapted as	
	Define criteria to assess (a) the	follows:	
	internal validity of included studies ( <i>e.g.</i> selection, performance, detection and attrition bias) and/or (b) other study quality measures ( <i>e.g.</i> reporting quality, power)	In addition we will assess reporting of: any blinding, any	
38.		randomization measures.	
		By use of <u>CAMARADES' study quality checklist, e.g</u> <sup>22</sup>	
		□By use of CAMARADES' study quality checklist, adapted	
		as follows:	
		Other criteria, namely:	
	Collection of outcome data		
		Gross macroscopic assessment of damage( Grading or	
		determining the area of articular cartilage with gross	
	For each outcome measure, define the type of data to be extracted ( <i>e.g.</i> continuous/dichotomous, unit of measurement)	morphological changes, ICRS scores, outerbridge scores,	
		either with or without staining methods)	
39.		Histological histochemical grading of changes in articular	
55.		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	If results are presented incomplete we will attempt to	
	(e.g. first extraction from graphs using	contact the author. If results are presented graphically	

	a digital screen ruler, then contacting authors)	only, data will be converted to numerical data using d ruler software.	igital			
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 ( <i>e.g.</i> 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 categor could be included. For the subgroup analysis a minimal of 3 studies per subgroup is required.				
	If a meta-analysis seems feasible/sensil	ple, specify (for each outcome measure):				
44.	The effect measure to be used ( <i>e.g.</i> mean difference, standardized mean difference, risk ratio, odds ratio)	If possible mean difference otherwise standardized m difference	ean			
45.	The statistical model of analysis ( <i>e.g.</i> random or fixed effects model)	Random effects model				
46.	The statistical methods to assess heterogeneity ( <i>e.g.</i> I <sup>2</sup> , Q)	<sup>2</sup>				
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 ( <i>e.g.</i> correction for multiple testing, correction for multiple use of control group)	Correction of p-value for the number of subgroup ana by Bonferroni-Holmes correction. Correction for multiple comparisons with the same co group by dividing the number of control animals by th number of comparisons with the control group.	ontrol			
50.	The method for assessment of publication bias	For MD: produce funnel plots and analyse these plots outcome measures with at least 15 studies. Funnel plot analysis will not be performed for SMDs because of the risk of funnel plot skewing.	for			
Final	Final approval by (names, affiliations): CR Hooijmans Date: 20/07/2016					