PROTOCOL FORMAT SYSTEMATIC REVIEW ANIMAL INTERVENTION STUDIES

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Item #	Section/ item	Description	Check for approval
	General		
1.	Title of the review	The translational gap in research about meniscus allograft	
2.	Authors (names, affiliations, contributions)	Jan J. Rongen† (*First reviewer, data analyses, manuscript preparation*) Gerjon Hannink† (*Second reviewer, supporting data analyses, reviewing manuscript*) Tony G. van Tienen† (*Reviewing manuscript Clinical perspective*) Carlijn R. Hooijmans ‡ (*methodological support, reviewing manuscript*) Judith van Luijk ‡ (*methodological support, reviewing manuscript*) † Orthopaedic Research Lab, Department of Orthopaedics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. ‡ SYRCLE at Central Animal Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands	
3.	Other contributors (names, affiliations, contributions)	Alice Tillema (*support building search strategy*) Medical library of the Radboud university medical centre Nijmegen, the Netherlands	
4.	Contact person + e-mail address	Jan Rongen, Jan.rongen@rabdoudumc.nl, tel 14930	
5.	Date of protocol registration	11-12-2014	
	Background		
6.	What is already known about this disease/ model/ intervention? Why is it important to do this review? INTRODUCTION	The knee menisci, two semilunar fibrocartilaginous disks, fulfill key biomechanical functions in the tibiofemoral (knee) joint.(Rongen, van Tienen et al. 2014) Unfortunately meniscal injuries are quite common, accompanied by acute symptoms such as joint line tenderness, impaired motion (e.g. locking), and joint effusions. Whereas first documented treatments embraced swift and total meniscectomy treating acute symptoms (Annandale 1889), less rigorous, tissue preserving interventions (e.g. partial meniscectomy and nowadays repair by suturing) were adopted after appreciating its clinical significance.(Abrams, Frank et al. 2013) The latter being the awareness that loss of meniscus tissue increases the risk for tibiofemoral osteoarthritis by inflicting pathologic contact stresses on cartilage surfaces. The amount of meniscal tissue lost demonstrated to be the strongest predictor of long-term onset of osteoarthritis.(Papalia, Del Buono et al. 2011) Total meniscectomy of the irreparable damaged meniscus thus poses a significant health problem. The meniscus allograft has been proposed as a promising treatment strategy for this problem.(Milachowski, Weismeier et al. 1989) The goal of this treatment was to prevent, and possibly even reverse, the progressive cartilage degeneration. However, clinical experience has redefined its indications towards short term decrease in pain, increase knee function, allow pain-free activities of daily living, and delay the progression of tibiofemoral osteoarthritis.(Rodeo 2001) Yet,	

		despite the considerable amount of literature controversies around its treatment effect still exist, particularly on the development of osteoarthritis.(Rosso, Bisicchia et al. 2014) This is however not in line with the results of the animal studies referred to by clinical studies (Hergan, Thut et al. 2011; Rosso, Bisicchia et al. 2014). Although it is not uncommon for animal studies not to correspond well to results from clinical trials it does raise the question to what extent results from animals can be translated to humans in meniscus related research. (Pound, Ebrahim et al. 2004) A systematic review analyzing preclinical studies will provide a complete and transparent overview of relevant information not directly visible from individual animal studies, and comparing this information with clinical studies would enable to map translational hurdles. Next, this review could extract recommendations to improve the methodological quality of the individual animal studies in order to increase the potential value of animal studies as a preparation for clinical applications. Therefore, it is the main aim of this systematic review to focus on the effect of meniscus allograft on the articular cartilage compared to its native counterpart in animals.	
	Objectives of this SR		
7.	Specify the disease problem of interest	Osteoarthritis after meniscectomy	
8.	Specify the population/species studied	Healthy animals	
9.	Specify the intervention/exposure	Meniscus allograft transplantation	
10.	Specify the control population	Sham operation OR not operated knee joint OR meniscectomized knee	
11.	Specify the outcome measures	Quantifiable outcome measures related to the articular cartilage degeneration/ damage in the knee joint: • Radiographic assessment (Kellgren and Lawrence) • Gross macroscopic degenerative changes of cartilage (e.g. India ink staining, according to Insall ea) • Histology (e.g. Mankin grading scale or Pineda) • Immunohistochemistry (e.g. cell apoptosis, collagen denaturation) • Histomorphometry (e.g. gag content, or cartilage thickness) • Cartilage-sensitive MRI, MRI with T2 mapping • Biomechanics, stiffness of articular cartilage	
12.	State your research question (based on points 7-11)	What is the effect of meniscus allograft on articular cartilage damage compared to its control (not operated / sham / meniscectomy) in healthy animals.	
	Methods:		
	Search and study identification		
13.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	• Pubmed • EMBASE	
14.	Define electronic search strategies (*e.g.* use the step by step search guide [1] and animal search filters [2, 3])	A search strategy composed of three elements (meniscus, allograft, and animals) will be developed in cooperation with experts from SYRCLE and information specialists from the medical library of the Radboud university medical centre Nijmegen, the Netherlands. To detect all animal studies in Pubmed and Embase, animal search filters will be used. A supplementary file containing the search strategy is attached: [bijlage]	
15.	Identify other sources for study identification	• Reference lists of included studies • Reference lists of relevant reviews	
16.	Define search strategy for these other sources	Same as supplementary file	
	Study selection phases		
17.	Define screening phases	• First selection phase based on title/abstract	

		• Second selection phase based on full text appraisal	
18.	Specify number of reviewers per screening phase	3; two independent investigators (JR, GH) and a third reviewer for dissolving any differences (CH)	
	Study selection criteria. Define all inclusion and exclusion criteria based on:		
19.	Type of study (design)	Inclusion criteria: • Intervention study • Controlled design • Primary study Exclusion criteria: • Non original articles (e.g. reviews, letters to editor, comments, proceedings, case reports, conference reports)	
20.	Type of animals/ population (*e.g.* age, gender, disease model)	Inclusion criteria: • Healthy animals Exclusion criteria: • No healthy animals	
21.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: • Meniscus allograft Exclusion criteria: • No meniscus allograft (autograft, xenograft etc) • Concomitant procedure on the cruciate ligament within the same knee joint (e.g. cruciate ligament reconstruction) • Concomitant procedure on the articular cartilage within the same knee joint (e.g. osteochondral autograft transfer)	
22.	Outcome measures	Inclusion criteria: • Quantifiable outcome measure on articular cartilage Exclusion criteria: • No quantifiable outcome measure on articular cartilage	
23.	Language restrictions	Inclusion criteria: • Exclusion criteria: •	
24.	Publication date restrictions	Inclusion criteria: • n.a. Exclusion criteria: • n.a.	
25.	Other	Inclusion criteria: • Peer reviewed Exclusion criteria: • No correct control group (not: meniscectomy, sham, unoperated) • Not peer reviewed • Duplicate publication	
26.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: First screening based on title/abstract 1. Type of study: not a primary intervention study 2. Type of intervention: not a meniscus allograft intervention 3. Type of population: not on healthy animals Selection phase: Second screening based on full text 1. Type of study; not a controlled interventional design 2. No correct control group (meniscectomy, sham, unoperated) 3. Outcome measures: no quantitative measure on articular cartilage 4. Type of intervention: concomitant surgical procedures within same	

		knee joint (e.g. ACL reconstruction, osteochondral autograft transfer)	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
27.	Study ID (*e.g.* authors, year)	• Authors • Journal • Year of publication • Original language	
28.	Study design characteristics (*e.g.* experimental groups, number of animals)	• Experimental groups • Type of control intervention • Number of animals in treatment and control groups • Duration of follow up, timing of data collection	
29.	Animal model characteristics (*e.g.* species, gender, disease induction)	• Species • Strain • Gender • Age • Weight at the beginning of the study	
30.	Intervention characteristics (*e.g.* intervention, timing, duration)	• Method of allograft preservation • Method of allograft sterilization • Method of allograft sizing • Surgical technique for approach • Fixation of allograft (suture, bone blocks, etc) • Procedures uni or bilaterally • Procedures (intervention/control) on medial or lateral compartment • Procedures (intervention/control) on left / right knee • Timing of intervention relative to meniscectomy (delayed or immediate) • If delayed intervention, time from meniscectomy to allograft transplantation • Postoperative rehabilitation (weight baring) regime	

31.	Outcome measures	• Outcome measure related to articular cartilage
		  ○ Radiographic assessment (Kellgren and Lawrence)
		  ○ Gross macroscopic degenerative changes of cartilage (e.g. India ink staining, according to Insall ea)
		  ○ Histology (e.g. Mankin grading scale or Pineda)
		  ○ Immunohistochemistry (e.g. cell apoptosis, collagen denaturation)
		  ○ Histomorphometry (e.g. gag content, or cartilage thickness)
		  ○ cartilage-sensitive MRI, MRI with T2 mapping
		  ○ Biomechanics, stiffness of articular cartilage	

32.	Other (*e.g.* drop-outs)	• Number of animals excluded for statistical analysis • Reason for excluding animals • Definition of complication • Complication rate • Definition of failures • Failure rate	
	Risk of bias assessment (internal validity)		
33.	Define criteria to assess the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias)	By use of SYRCLE's Risk of Bias tool [4]	

	Collection of outcome data		
34.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/ dichotomous, unit of measurement)	(Quantitative) Measures related to the articular cartilage in the knee joint: • Radiographic assessment (Kellgren and Lawrence) [grade 0-4] • Scoring systems for macroscopic grading of cartilage damage [semi-continuous] • Scoring systems for macroscopic grading of osteophytes [semi-continuous] • Microscopic scoring of cartilage alterations (Mankin) [semi-continuous] • Microscopic scoring via immunohistochemistry (cell apoptosis/collagen denaturation) [continuous] • Microscopic scoring via Histomorphometry (e.g. gag content, or cartilage thickness) [continuous] Failures (definition and amount) Complications (definition and amount)	
35.	Methods for data extraction/retrieval	Extraction from results section, if needed first contacting authors, then extraction from graphs using plot digitizer	
	Data analysis/synthesis. Specify (per outcome measure):		
36.	How you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Descriptive summary of (quantitative) measures on articular cartilage damage. If possible a meta analysis.	
37.	How the decision as to whether a meta-analysis will be performed will be made	Based on the amount of sufficient comparable articles with specified quantitative outcome measures that can be included, at least a minimum of three eligible articles.	
	If a meta-analysis seems feasible/sensible. For each outcome measure specify:		
38.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	Standardized Mean Difference (Difference in means of outcome between intervention and control group divided by the pooled standard deviation). If possible a Normalized Mean Difference.	
39.	The statistical model of analysis (*e.g.* random or fixed effects model)	random effects model, Forest plots will be used to display the mean overall effect sizes, together with effect sizes for subgroups	
40.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2 (the proportion of total variance explained by heterogeneity)	
41.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	• Species (large/small) • Procedures on medial or lateral compartment (medial / lateral) • Surgical technique / fixation of allograft (bone blocks / suture) • Method of allograft preservation / sterilization / sizing • Fixation of allograft (suture, bone blocks)	
42.	The method for assessment of publication bias	Creating a funnel plot in Revman software, trim and fill if possible	
43.	Any sensitivity analysis you propose to perform	Post hoc subgroup analysis (based on excluding the studies with a low overall quality score). Next, test for a effect of possible interactions.	

Final approval by (names, affiliations):

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