Supplementary Table 2: SYRCLE Protocol

Systematic Review Protocol for Animal Intervention Studies

Format by SYRCLE (www.syrcle.nl)
Version 2.0 (December 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Mesenchymal stem cells and their application to rotator cuff pathology: a meta-analysis of pre-clinical animal and human studies	
2.	Authors (names, affiliations, contributions)	Nicolas Morton-Gonzaba Daniel Carlisle Kevin Chorath Alvaro Moreira	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	Alvaro Moreira: moreiraa@uthscsa.edu	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	CAMARADES	
8.	Registration number (if applicable)	N/A	
9.	Stage of review at time of registration	Preliminary searches Piloting study selection Formal screening with final search criteria	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Rotator cuff tendon tears are the most common tendon injury in adults. Although surgical tendon repair is one of the most common orthopaedic interventions, surgical failure varies from 20% to 90%. In lieu of their application to various disease/injury processes and the research being conducted, mesenchymal stem cell therapy is an attractive alternative to overcome current treatment deficits.	
	Research question		

	"http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3265183/pdf/LA-11-087.pdf" and animal search filters[2 HYPERLINK "http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104815/pdf/LA-09-117.pdf"0 HYPERLINK "http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104815/pdf/LA-09-117.pdf", 21)		
19.	Identify other sources for study identification	X Reference lists of included studies ☐Books X Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
20.	Define search strategy for these other sources	Screening the reference lists for relevant titles and screening the abstracts of these relevant titles	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	First phase screening based on title and abstract Second phase full-text screening of the eligible articles	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Two investigators (N. Morton-Gonzaba and D. Carlisle) will independently screen all the abstracts/full texts for the inclusion criteria. Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira).	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Animal intervention studies (with control group) regardless of the methodological quality; Human clinical trials-any phase Exclusion criteria: Non-intervention studies, no control group	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Animal models of experimental rotator cuff injury Humans (all ages) with rotator cuff injury	

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		Exclusion criteria: In vitro	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Administration of regenerative cells/ cell-free products– all dosages, timing, delivery routes, and frequency	
26.	Outcome measures	Primary outcome: Imaging (including, but not limited to: x-ray, ultrasound, CT/MRI) and/or Range of motion Secondary outcome: Histologic/Microscopic analyses of wound healing Gene/protein expression inflammation, fibrosis, angiogenesis, wound healing Safety, Long-term outcome	
27.	Language restrictions	All languages will be included	
28.	Publication date restrictions	None	
29.	Other	N/A	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: title and abstract screening 1. Not a primary study 2. Not an *in vivo* animal/human study 3. No rotator cuff injury 4. No regenerative cell or cell-free product treatment 5. No animal control group	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, journal, title, year, language, contact author e-mail	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Animal: Number of animals in experimental and control groups; induction of rotator cuff injury Human: number, experimental groups, inclusion/exclusion criteria	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Animal: species, strain, age, gender Human: age, gender	

34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Source, dose, route of delivery, timing, and frequency of regenerative cells or cell-free product	
35.	Outcome measures	Per primary and secondary outcomes of interest	
36.	Other (*e.g.* drop-outs)	Reason of exclusion	
	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	Two investigators (N. Morton-Gonzaba and D. Carlisle) will independently screen all the abstracts/full texts for the inclusion criteria. Differences of opinion in either phase that cannot be resolved by discussion will be resolved by consulting a third investigator (A. Moreira).	
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)	X By use of SYRCLE's Risk of Bias tool HYPERLINK "http://www.biomedcentral.com/1471-2288/14/43/abstract"4 HYPERLINK "http://www.biomedcentral.com/1471-2288/14/43/abstract" ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/15060322"e.g HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/15060322" HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/15060322"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)	Primary/Secondary outcome: continuous and/or categorical data	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Extraction from text, tables, and figures (GetData Graph Digitizer) Contact authors in case of missing data	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Two investigators (N. Morton-Gonzaba and D. Carlisle) will independently screen all the abstracts/full texts for the inclusion criteria. Differences of opinion in either phase that cannot be resolved	

		by discussion will be resolved by consulting a third investigator (A. Moreira).	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	If the outcome measures extracted from eligible studies are sufficient we will conduct meta analyses.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed		
	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)	Continuous outcomes will be analysed using standardized mean differences (95% CI)	
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)	Meta-regression analyses will be performed to examine heterogeneity on outcomes including: animal/human age, sex, type and tissue source of regenerative cell or product, timing, frequency, dosing of administration, route of cell administration, use of co-interventions	
48.	Any sensitivity analyses you propose to perform		
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)		
50.	The method for assessment of publication bias	Funnel plots and Egger's test	
Final approval by (names, affiliations):		Nicolas Morton-Gonzaba Daniel Carlisle Kevin Chorath Alvaro Moreira University of Texas Health San Antonio	Date: Feb 18, 2019