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	Systematic review on surgical embryo transfer in laboratory mice.	
2.	Authors (names, affiliations, contributions)	Mattea Durst (Centre for Surgical Research, University of Zurich): Study design, literature screening, data extraction and analysis, manuscript Paulin Jirkof (Centre for Surgical Research and Department Animal Welfare and 3R, University of Zurich): Study design, literature screening, data extraction and analysis, manuscript Petra Seebeck (Zurich integrative Rodent Physiology (ZIRP), University of Zurich): Literature screening, data extraction, manuscript Felix Gantenbein (Institute of Laboratory Animal Science, University of Zurich): Literature screening, data extraction, manuscript Cathalijn Leenaars (Institute for Laboratory Animal Science, Hannover Medical School): Study design, manuscript	
3.	Other contributors (names, affiliations, contributions)	-	
4.	Contact person + e-mail address	Mattea Durst, mattea.durst@usz.ch	
5.	Funding sources/sponsors	DFG FOR2591	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	14-04-2020, SYRCLE website.	
8.	Registration number (if applicable)	-	
9.	Stage of review at time of registration	Searches performed; screening not yet started	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Murine embryo transfer is a common procedure in laboratory animal science. Embryo transfers (ET) are being used in experiments as well as for breeding purposes and rederivation in animal husbandry. In principle, an ET is conducted by withdrawing embryos from a female donor mouse and transferring them to a female recipient mouse. The embryos can be either inserted in the recipient via a non-surgical vaginal approach or a surgical procedure directly into the upper reproductive tract. The latter is the standard method	

		where a laparotomy with a surgical access through the abdominal wall is conducted in mice under general anaesthesia. The severity of this method is classified as moderate under EU directive 2010/63. For surgical embryo transfers there is no published standardized protocol concerning perioperative care, analgesia or anaesthesia. This systematic review will provide a broad overview on the surgical embryo transfer in mice. More precisely, we will aim to gather knowledge on the incidence and quality of applied refinement in the surgical embryo transfer. It will reveal measures of improvement and help to establish recommendations on best practice.	
	Research question		
11.	Specify the disease/health problem of interest	No disease or health problem is studied.	
12.	Specify the population/species studied	Laboratory mouse.	
13.	Specify the intervention/exposure	Surgical embryo transfer.	
14.	Specify the control population	Any or none.	
15.	Specify the outcome measures	For the study selection: Any. For this SR: we will record anaesthesia and analgesia (administration route and type of medication, dosage, frequency, other pain management techniques), surgical technique, peri-operative care, refinement measures; reporting of animal related information (reporting quality), measurements on reproduction success and efficacy of pain alleviating measures.	
16.	State your research question (based on items 11-15)	How has surgical embryo transfer been performed in mice? Subquestions: - What procedures are most often used and described as effective to ensure a consistent wellbeing for animals after surgery? - Do these procedures have an impact on reproductive performance?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	☐ MEDLINE via PubMed **X** Web of Science **X** SCOPUS **X** EMBASE **X** Other, namely: Medline via OVID ☐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])	The search string can be found in the attached document and consists of 2 search elements concerning the investigated population (mice) and the intervention (surgical embryo transfer).	

19.	Identify other sources for study identification	X 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)	Removal of duplicates. Screening of title and abstract, removing of articles according to criteria below. Screening of full text.	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Removal of duplicates will be done by one person. 2 reviewers for the remaining phases. Discrepancies will be resolved by discussion, if needed with a third reviewer.	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Original experimental data, in vivo studies Exclusion criteria: Other study types.	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Mice (*Mus musculus)* Exclusion criteria: Other Species.	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Surgical embryo transfer. Exclusion criteria: Non-surgical embryo transfer, only embryo removal, no intended survival of recipient mouse, no intended birth of embryos.	
26.	Outcome measures	Inclusion criteria: Any Exclusion criteria: None.	
27.	Language restrictions	Inclusion criteria: Any Exclusion criteria: None.	
28.	Publication date restrictions	Inclusion criteria: None. Exclusion criteria: None.	
29.	Other	Inclusion criteria: None. Exclusion criteria: None.	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase within title and abstract: 1. No mice 2. No original data 3. No surgical embryo transfer Selection phase within full text: 1. No mice 1. No original in vivo data 2. No full embryo transfer (with donor and recipient mouse)	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	ID, first author, title, year, journal, issue, pages, language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Number of animals, background/purpose of ET (experimental or husbandry)	

33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Sex, strain, housing condition (temperature, cage, enrichment), handling technique, mortality, end of experiment and fate of the used animals.	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	surgical procedure (asepsis, anaesthesia), analgesia, monitoring, peri-operative care, non-pharmalogical measures, refinement measures	
35.	Outcome measures	Reproductivity measurements, parameters testing efficacy of pain/stress reducing measures	
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	See 38. and 41.	
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: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: X Other criteria, namely: No formal risk of bias assessment will be done as we will include studies without a control condition to evaluate the potential bias against. Study quality will be evaluated on the study characteristics; is information available or not and if so, what is the content.	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Study characteristics and outcome measures named in 31.-35. will be recorded in a table as provided in the reference and summarised qualitatively.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Study characteristics and data will be extracted from text and graphs. Characteristics provided by referencing another publication will be tracked for one level. If the information is not provided in the referenced article (indirect referencing) it is recorded as not reported.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	One reviewer will extract data and a random sample of 5% of data will be analysed by a second reviewer.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	The study characteristics and outcome measures (31.-35.) will be tabulated as qualitative data, whenever possible data will be categorized. When suitable, outcome measures are additionally recorded as quantitative information (e.g. analgesic dosage, animal numbers). All results will be used to give a descriptive overview on surgical embryo transfer in laboratory mice.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	No 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)	-	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	-	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	-	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	-	
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	-	
Final approval by (names, affiliations):			Date: