SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check appro
	A. General		
1.	Title of the review	**The efficacy of anti-adhesive barriers in preventing adhesion formation and reformation in animals: a systematic review and meta-analysis**	
2.	Authors (names, affiliations, contributions)	Chema Strik, Martijn Stommel, Richard ten Broek, Prof. Harry van Goor, department of surgery, Radboud university medical centre Kim Wever, SYRCLE, Radboud university medical centre	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	chema.strik@radboudumc.nl	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration		
8.	Registration number (if applicable)	NA	
9.	Stage of review at time of registration	Before the search was carried out we specified our methodology in a protocol	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?		
	Research question		
11.	Specify the disease/health problem of interest	Adhesion formation and reformation	
12.	Specify the population/species studied	All animals used in experiment meeting our inclusion criteria	
13.	Specify the intervention/exposure	Anti-adhesive barriers and surgical technique	
14.	Specify the control population	No intervention, saline, placebo	
15.	Specify the outcome measures	Incidence of adhesion Adhesion score Planimetrical data Number of adhesions against ischemic buttons	
16.	State your research question (based on items 11-15)	1. To assess the reproducibility of the different animal models of adhesion formation. 2. To assess the quality of the different adhesion formation animal studies performed. 3. To assess the effectiveness of anti-adhesive barriers and surgical technique in adhesion formation prevention in animal models.	
	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 [1] and animal search filters [2, 3])	***Disease of interest:*** **Adhesion:** (("Tissue Adhesions"[Mesh] OR “Tissue adhesions” [Tiab] OR “Tissue Adhesion” [tiab] OR “Surgical Adhesions” [tiab] OR “Surgical adhesion” [tiab]) ***AND*** **Peritoneum:** ("Peritoneum"[Mesh] OR “peritoneum” [tiab] OR "Mesentery"[Mesh] OR “Peritoneum, Visceral” [tiab] OR “Visceral Peritoneum” [tiab] OR “Peritoneum, Parietal” [tiab] OR “Parietal Peritoneum” [tiab] OR “Cavity, Peritoneal” [tiab] OR "Abdomen"[Mesh] OR “abdomen” [tiab] OR “abdomens” [tiab] OR "Abdominal Cavity"[Mesh] OR “Abdominal Cavities” [tiab] OR “Cavities, Abdominal” [tiab] OR “Cavity, Abdominal” [tiab] OR “Cavitas abdominis” [tiab] OR “intra-abdominal” [tiab] OR “intraabdominal” [tiab] OR “intraperitoneally” [tiab] OR “intra-peritoneally” [tiab])) ***OR*** **Gecombineerde termen:** (“peritoneal adhesion” [tiab] OR “peritoneal adhesions” [tiab] OR “abdominal adhesion” [tiab] OR “abdominal adhesions” [tiab] OR “intra-abdominal adhesion” [tiab] OR “intra-abdominal adhesions” [tiab] OR “intraabdominal adhesion” [tiab] OR “intraabdominal adhesions” [tiab]) **intervention:** "Seprafilm" [tiab] ”Sepracoat” [tiab] OR "INTERCEED" [tiab] OR “Repel-CV” [tiab] OR “Gore-tex surgical membrane” [tiab] OR “Gore tex surgical membrane” [tiab] OR "Polytetrafluoroethylene"[Mesh] OR “GORE-TEX” [tiab] OR “GORE TEX” [tiab] OR “Goretex” [tiab] OR “Prevadh” [tiab] OR "SuperSeal" [tiab] OR “Oxidized regenerated cellulose” [tiab] OR “cellulose” [tiab] OR “tc7” [tiab] OR “cellulose” [tiab] OR “Hyaluronate carboxymethylcellulose” [tiab] OR “carboxymethylcellulose” [tiab] OR “hyaluronan” [tiab] OR “hyaluron” [tiab] OR “hyaluronic acid” [tiab] OR "Adcon-P" [tiab] OR “Adept” [tiab] OR “Icodial” [tiab] OR “Baxter Brand of Icodextrin” [tiab] OR “Extraneal” [tiab] OR "icodextrin" [tiab] OR “Sepracoat” [tiab] OR "Seprafilm" [tiab] OR “Tisseel” [tiab] OR "Fibrin Tissue Adhesive" [Mesh] OR “Fibrin Adhesive” [tiab] OR “Fibrin Glue” [tiab] OR “Fibrinogen Adhesive” [tiab] OR “Fibrin Sealant System” [tiab] OR “Crosseal” [tiab] OR “Fibrin Klebe System Immuno” [tiab] OR “Transglutine” [tiab] OR “Fibrin Sealant” [tiab] OR “Tissel” [tiab] OR “Tissucol” [tiab] OR “Beriplast” [tiab] OR “Fibrin Seal” [tiab] OR “Sprayshield” [tiab] OR “Spraygel” [tiab] OR “PEG” [tiab] OR	

		“polyethylene glycol” [tiab] OR “Intercoat” [tiab] OR "intergel" [tiab] OR “Sepraspray” [tiab] OR "crystalloid solutions" [tiab] OR “Ringer’s lactate” [tiab] OR "Isotonic Solutions"[Mesh] OR "Sodium Chloride"[Mesh] OR “Sodium Chloride” [tiab] OR “NaCl” [tiab] OR “Saline Solution” [tiab] OR “adhesiolysis” [tiab] Animal search filter as published by SYRCLE	
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	Not applicable	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Title/abstract screening + full text assessment	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Two persons screening on title/abstract Discrepancies will be resolved with the help of a third person Two persons full-text extraction phase Discrepancies will be resolved with the help of a discussion	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: A standardized model in which a standard injury is performed on the peritoneum, similar for each group, after which an intervention (gas / gel / film etc.) is carried out, after which in a consistent manner, intra-peritoneal adhesions are measured in the abdomen. Exclusion criteria:	
24.	Type of animals/population (*e.g.* age, gender, disease model)	All animals and disease models fulfilling the in and exclusion criteria	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Not applicable	
26.	Outcome measures	Inclusion criteria: Incidence of adhesion Adhesion score Planimetrical data Number of adhesions against ischemic buttons Exclusion criteria: Other or no outcome measures	
27.	Language restrictions	Inclusion criteria: Exclusion criteria: Chinese, Cyrillic (including Russian) and Arabic	
28.	Publication date restrictions	Not applicable	
29.	Other		
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: screening title and abstract ▪ Not an animal study ▪ Reviews ▪ Letter to the editor	

		▪ Abstract only ▪ Not an adhesion-model ▪ Duplication of data from another article included Selection phase: full-text assessment ▪ No numerical or graphical data on primary outcome measures ▪ Not an adhesion reformation model ▪ Not the same adhesion reformation model between groups	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Author and year	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Number of experimental groups Number of control groups Number of animals used in each group	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	▪ Species ▪ Strain ▪ Sex of animals ▪ Weight of animals ▪ Age of animals ▪ Adhesion formation models ▪ Cecal abrasion ▪ Cecal abrasion + lateral sidewall ▪ Uterine horn ▪ Ischemic buttons ▪ Bowel anastomosis model ▪ Cecal ligation ▪ Cecal ligation with puncture ▪ Device used for injuring tissue ▪ Sharp • Scalpel • Dissecting scissors ▪ Blunt • Gauze • Brush ▪ Coagulation • Unipolar • Bipolar • Ultrasonic ▪ Sutures • Absorbable monofilament • Absorbable multifilament • Non-absorbable monofilament • Non-absorbable multifilament ▪ Chemical device • Latex powder • Starch powder ▪ Alcohol ▪ Control of injury induced	

		▪ Analgesia used ▪ Antibiotics used peri-operatively ▪ Peri-operative fluid management ▪ Peritonitis ▪ Analgesia used ▪ Contaminated model ▪ All risk of bias parameters ▪ Type of adhesion scoring system ▪ Interval of scoring system ▪ Time interval of surgery ▪ Type of anti-adhesive barrier (gel, broad coverage solution, film) ▪ Number of ml of anti-adhesive barrier ▪ Commercial available anti-adhesive barriers ▪ Type of working mechanism (anti-inflammatory, anti-coagulatory etc.)	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	All intraperitoneal anti-adhesive barriers, surgical technique	
35.	Outcome measures	See point 26	
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	Two reviewers Discrepancies will be resolved after 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: We devised an 8-point scoring system to assess the methodological quality of included articles based on the tool published by Hooijmans et al. (1) Ethical statement was defined as the mentioning of an approved protocol by an ethical committee. If no statement regarding the approval of a protocol was reported we defined this as not specified. (2) Adequate allocation sequence generation was defined as a process where a computer generated the sequence or blinded envelopes were used. If only the word randomization was stated in the article we defined this as not specified. (3) Similar groups at baseline was defined as the groups having equal adhesions as presented in a table or a statement about the difference between the groups at the time of adhesiolysis. Animals should have been reoperated and sacrificed at similar time intervals and should be of the same gender or each group should contain similar proportions of males and females. (4) Blinded from treatment allocation was defined as measures taken to blind the surgeon from treatment allocation by using placebo barriers or a third person applying the control intervention or adhesion barrier. If there was no statement in the article regarding blinded treatment allocation it was defined as unknown. (5) Method of serosal injury specified and standardized is defined as the method and material used to induce serosal injury was specified, if the injury was standardized and if the method of adhesiolysis was	

		specified. (6) Random outcome assessment was defined as a process where the order in which the animals were being assessed for the outcome measure was randomized. If the word randomization was stated it was defined as yes, if there was no statement regarding the randomization of outcome assessment it was defined as not specified. (7) Blinded outcome assessment was defined as the person assessing the outcome variable being blinded from which treatment the animal received. (8) Incomplete outcome data adequately addressed was defined as the total number of animals was stated and if it matched with the number of animals stated in the results. A statement regarding the exclusion or mortality of animals and the number of animals was only specified in the results section was also deemed adequate. The reasons for exclusion and mortality were required and the mortality of the animals should be less than 10%. Studies meeting 7 or 8 methodological criteria of risk of bias assessment were considered to have a low risk of bias. ☐By use of CAMARADES' study quality checklist, e.g. [5] ☐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)	Incidence of adhesion: Dichotomous data Adhesion score: continuous data Planimetrical data: continuous data Number of adhesions against ischemic buttons: dichotomous data	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Data from a table will be used as a first extraction site, the second site will be the result section and the third site will be an assessment of graphs with the help of ImageJ.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Two reviewers Discrepancies will be resolved after discussion	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	For all outcome measures a meta-analysis will be carried out	
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)	Dichotomous data: Risk Ratio Continuous data: 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)	Q-value and I^2	

47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	▪ Species ▪ Strain ▪ Sex of animals ▪ Cecal abrasion ▪ Cecal abrasion + lateral sidewall ▪ Uterine horn ▪ Ischemic buttons ▪ Bowel anastomosis model ▪ Cecal ligation ▪ Cecal ligation with puncture ▪ Control of injury induced ▪ Analgesia used ▪ Antibiotics used peri-operatively ▪ Peri-operative fluid management ▪ Peritonitis ▪ Analgesia used ▪ Contaminated model ▪ All risk of bias parameters ▪ Type of adhesion scoring system ▪ Interval of scoring system ▪ Time interval of surgery ▪ Type of anti-adhesive barrier (gel, broad coverage solution, film) ▪ Number of ml of anti-adhesive barrier ▪ Commercial available anti-adhesive barriers ▪ Type of working mechanism (anti-inflammatory, anti-coagulatory etc.)	
48.	Any sensitivity analyses you propose to perform	Sensitivity analysis will be performed	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Correction for multiple use of control group by dividing the number of control animals by the number of experimental groups, a minimum number of 2 animals will be used. Correction for 100% incidence in both the control and intervention group by subtracting 0.5 in both groups. The most effective barrier will be incorporated in analysis in case of multiple experimental groups. In case of multiple control studies, the group with no intervention will be incorporated in the meta-analysis	
50.	The method for assessment of publication bias	Visual inspection of funnel plots followed by an Egger's regression analysis.	

Final approval by (names, affiliations):

Date: 1-1-2014

Chema Strik (Surgery)
Martijn Stommel (Surgery)

Richard ten Broek (Surgery)
Harry van Goor (Surgery)
Kim Wever (SYRCLE)