Benefits, challenges and tools

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Radboudumc

Disclosure

I am a preclinical systematic review enthusiast

Benefits of preclinical SRs

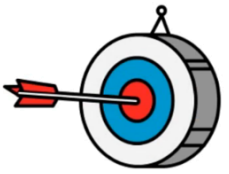
PROVIDE OVERVIEW OF AVAILABLE EVIDENCE

IDENTIFY KNOWLEDGE GAPS

CRITICAL APPRAISAL OF STUDY QUALITY

IDENTIFY FACTORS INFLUENCING TREATMENT EFFICACY

INFORM EXPERIMENTAL DESIGN OF ANIMAL CLINICAL STUDIES



Overview and knowledge gaps

Macleod et al. 2005
melatonin in stroke - 13 studies

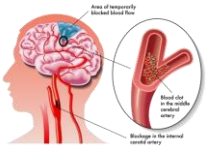


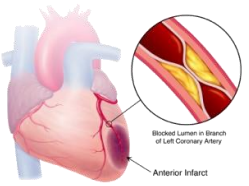
Table 2. Design characteristics of included studies

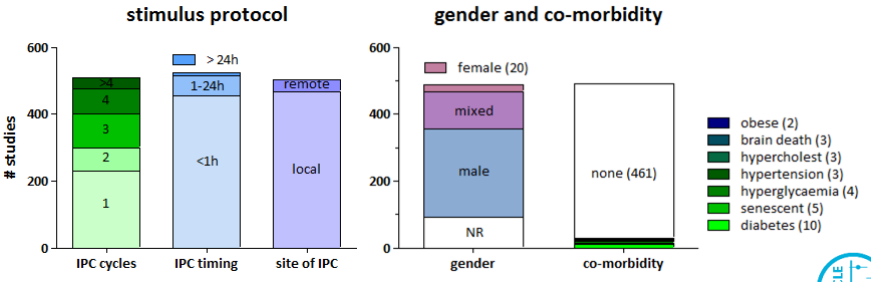
Publication	Gender	n (C)	n (Rx)	Dose range (mg/kg)	Doses in first 24 hr	Time to treatment	Anaesthetic	Permanent or focal ischaemia	Route of drug delivery	Outcome measure
Joo (1998)	Male	6	6	2.5	4	−15 min	Chloral hydrate	Temporary	i.p.	Inf. vol.
Kilic (1999)	Nk	8	6	4	2	0 min	Ketamine	Temporary	Intravenous	Comb
Ling (1999)	Male	9	31	2.5–10	3	−15 min	Chloral hydrate	Temporary	Subcutaneous	Inf. vol.
Peker (2000)	Nk	2	6	2.5	4	−20 min	Not known	Permanent	i.p.	Comb
Borlongan (2000)	Male	11	11	23.2	1	0 min	Halothane	Temporary	Oral	Comb
Sinha (2001)	Male	7	8	20	4	0 min	Chloral hydrate	Temporary	i.p.	Comb
Pei (2002a)	Male	14	61	1.5–50	1	−30 min	Pentobarbital	Temporary	i.p.	Inf. vol.
Gupta (2002)	Male	12	12	20	4	0 min	Chloral hydrate	Temporary	i.p.	Comb
Pei (2002b)	Male	21	23	5–50	1	−30 min	Pentobarbital	Permanent	i.p.	Inf. vol.
Sun (2002)	Male	6	18	2.5–10	3	−15 min	Chloral hydrate	Temporary	i.p.	Inf. vol.
Pei (2003)	Male	44	57	5–15	1–3	0–120 min	Pentobarbital	Temporary	i.p.	Inf. vol.
Torii (2004)	Male	11	10	5	1	0 min	Halothane	Temporary	Oral	Inf. vol.
Lee (2004)	Male	16	16	5	1	90 min	Halothane	Temporary	Intravenous	Comb

Number of animals in control group [n (C)]; number of animals in experimental group [n (Rx)]; dose range; number of doses given in first 24 hr; interval from onset of ischaemia to start of treatment; anaesthetic used; and outcome measure used; Nk, not known; i.p., intraperitoneal.

Overview and knowledge gaps

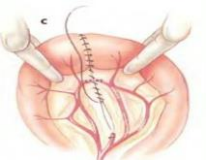
Wever et al. 2015
Ischemic conditioning in MI
500 studies

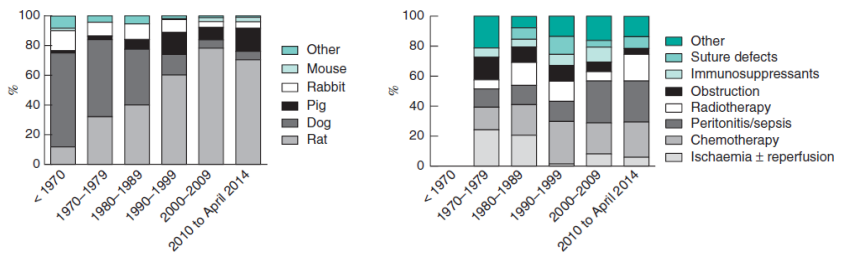




Overview and knowledge gaps

Yauw et al. 2014
Experimental intestinal anastomosis
1300 studies

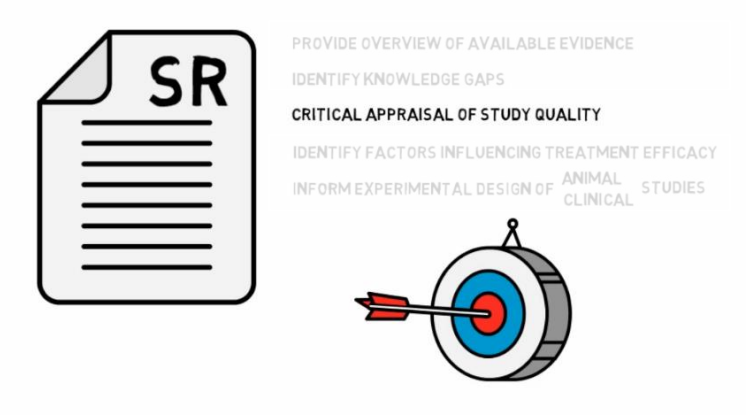




a Animal species

b Type of compromising factor

Aims of preclinical systematic reviews



What is quality?

External validity

Reproducibility

Power

Precision

Internal validity

Etc.

- How valid are the results for the target population?
- Threatened by bias

SYRCLE's Risk of Bias tool

Table 2 SYRCLE's tool for assessing risk of bias

Item	Type of bias	Domain	Description of domain	Review authors judgment
1	Selection bias	Sequence generation	Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups.	Was the allocation sequence adequately generated and applied? (*)
2	Selection bias	Baseline characteristics	Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment.	Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3	Selection bias	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	Was the allocation adequately concealed? (*)
4	Performance bias	Random housing	Describe all measures used, if any, to house the animals randomly within the animal room.	Were the animals randomly housed during the experiment?
5	Performance bias	Blinding	Describe all measures used, if any, to blind trial caregivers and researchers from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?

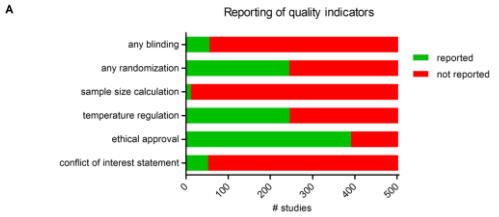
Hooijmans et al. (2014) BMC Medical Research Methodology 14:43

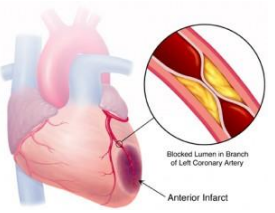
Risk of Bias tool (2/2)

6	Detection bias	Random outcome assessment	Describe whether or not animals were selected at random for outcome assessment, and which methods to select the animals, if any, were used.	Were animals selected at random for outcome assessment?
7	Detection bias	Blinding	Describe all measures used, if any, to blind outcome assessors from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Was the outcome assessor blinded?
8	Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized animals), reasons for attrition or exclusions, and any re-inclusions in analyses for the review.	Were incomplete outcome data adequately addressed? (*)
9	Reporting bias	Selective outcome reporting	State how selective outcome reporting was examined and what was found.	Are reports of the study free of selective outcome reporting? (*)
10	Other	Other sources of bias	State any important concerns about bias not covered by other domains in the tool.	Was the study apparently free of other problems that could result in high risk of bias? (*)

*Items in agreement with the items in the Cochrane Risk of Bias tool.

A challenge...

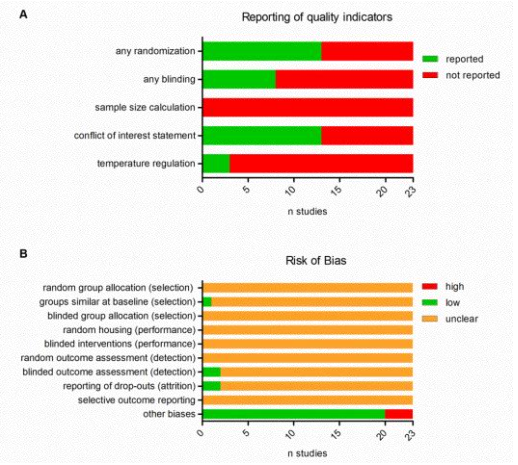


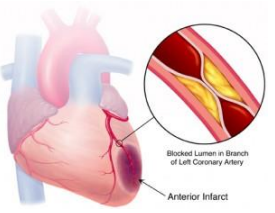


Poor reporting

Wever et al. 2015 – ischemic preconditioning in MI

Across interventions...

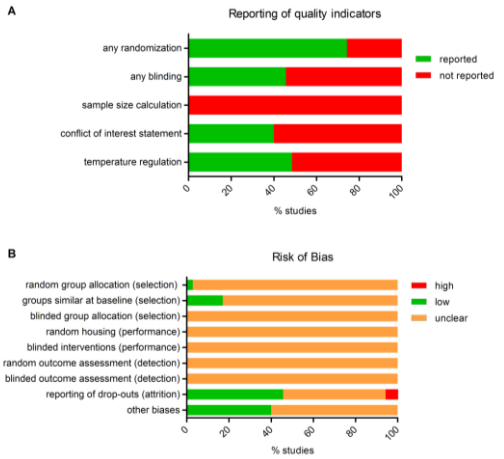




Poor reporting
Unclear risks of bias

Wever et al. under review – metformin in MI

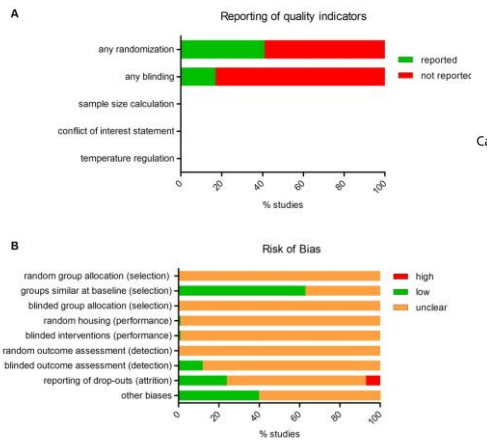
Across disease models...

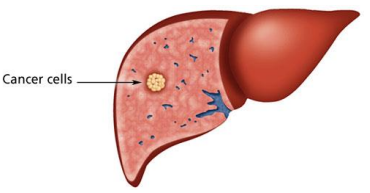


Poor reporting
Unclear risks of bias

Jonker et al. 2016 – ischemic postconditioning in renal IRI

Across research fields...

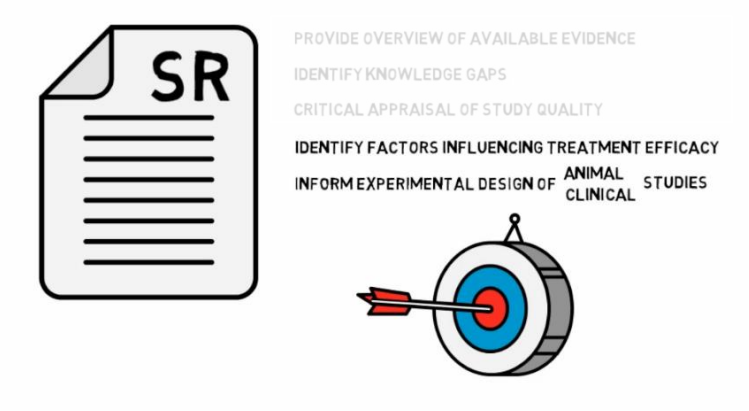




Poor reporting
Unclear risks of bias

Hooijmans et al. 2016 – anaesthetic drugs and cancer metastases

Benefits of preclinical SRs



Meta-analysis

=

Analysis of analyses

=

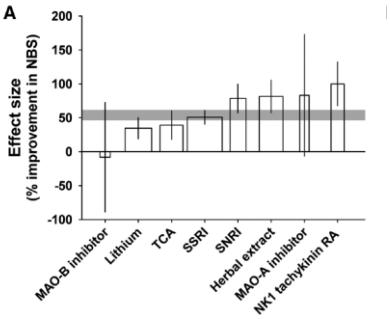
(statistical) combination of data from primary studies

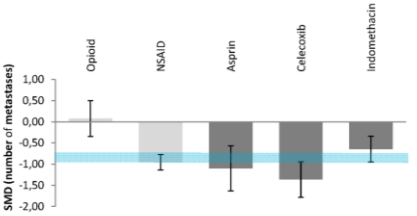
Aims of meta-analysis of animal study data:

- Evaluate the efficacy of an intervention (focus on direction)
- Explore heterogeneity to generate new hypotheses
- Guide the design of future (pre-)clinical trials
- Find new results (without having to use more animals)

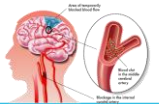
Factors influencing treatment efficacy

Drug classes

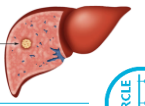




McCann et al. 2014 – antidepressants in stroke

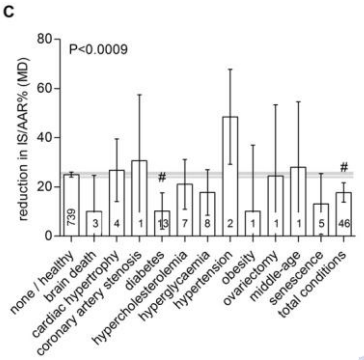


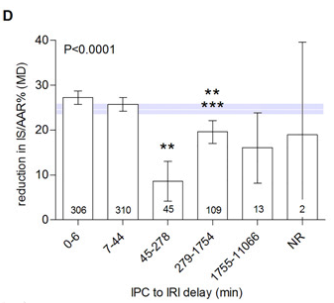
Hooijmans et al. 2016 – anaesthetic drugs and cancer metastases

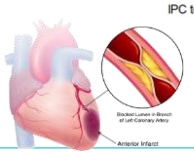


Factors influencing treatment efficacy

Animal model and intervention timing



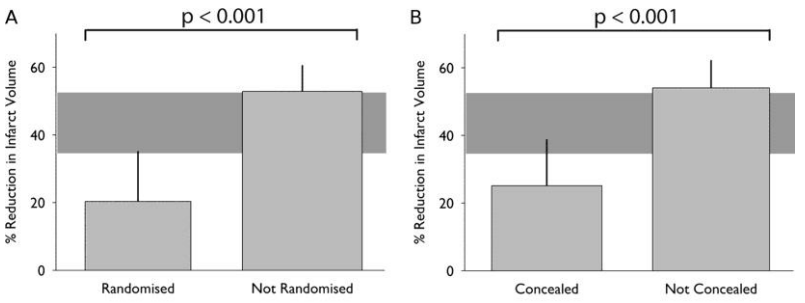




Wever et al. 2015 – ischemic preconditioning in MI

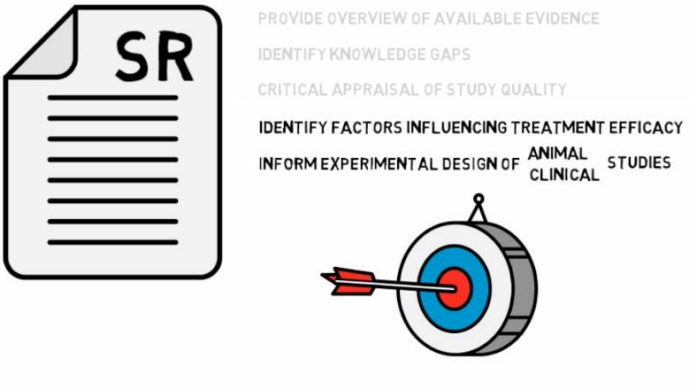
Factors influencing treatment efficacy

Measures to reduce bias!



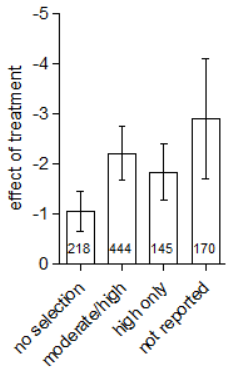
Macleod et al. *Stroke* 2008

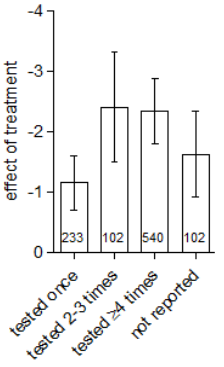
Benefits of preclinical SRs



Informing animal studies

Reducing animal use





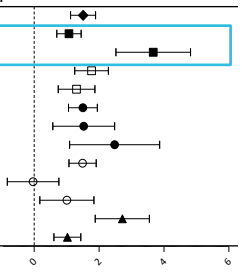
Groenink et al. 2015 – anxiolytics in guinea pig separation induced anxiety model

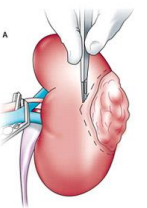
Informing clinical trials: trial design?

current clinical trials on RIPC in renal IRI are using similar preconditioning protocols, namely fractionated IPC stimuli, and a short delay between IPC and index ischemia (early window of protection). The current review indicates that even though this approach might be effective, efficacy could be even higher in the late window of protection. Future studies should be designed to

Table S3 | Subgroup analysis serum creatinine

Subgroup	n experiments	n studies	n IRI only	n IRI + IPC	SMD and 95% confidence interval
overall	62	33	512	492	1.54 [1.16, 1.93]
early	47	25	413	384	1.10 [0.72, 1.48]
late	15	9	99	108	3.53 [2.45, 4.60]
continuous	32	18	257	250	1.77 [1.25, 2.29]
fractionated	30	20	255	242	1.31 [0.74, 1.87]
LIPC	51	29	421	390	1.47 [1.03, 1.90]
RIPC	6	3	60	60	1.53 [0.57, 2.48]
LIPC + RIPC	5	1	31	42	2.48 [1.09, 3.87]
male	42	22	345	339	1.51 [1.09, 1.93]
female	2	2	17	18	-0.03 [-0.83, 0.76]
male + female	11	4	87	81	1.13 [0.25, 2.02]
mouse	22	12	173	170	2.72 [1.88, 3.55]
rat	35	18	303	286	1.02 [0.61, 1.44]





Wever et al. 2012

Informing clinical trials: start a trial?

Hypothermia in ischaemic stroke models

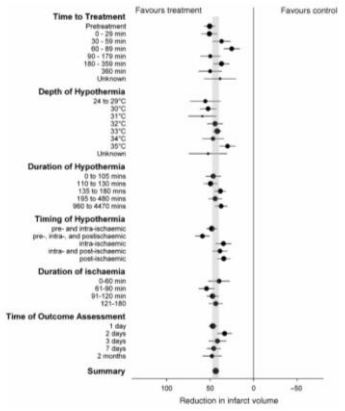


Fig. 4 Point estimate of effect on infarct size and 95% CI by duration of ischaemia in models of reperfusion, time to treatment, depth of hypothermia, duration of hypothermia, timing of hypothermia and time of outcome assessment. The grey band indicates the global estimate and its 95% CI.

Conclusion

In animal models of focal cerebral ischaemia, hypothermia improves outcome by about one-third under conditions that may be feasible in the clinic, with even modest cooling resulting in a substantial improvement in outcome. Cooling is effective in animals with co-morbidity and with delays to treatment of 3 h. Large randomized clinical trials testing the efficacy of moderate hypothermia in patients with acute ischaemic stroke are warranted.

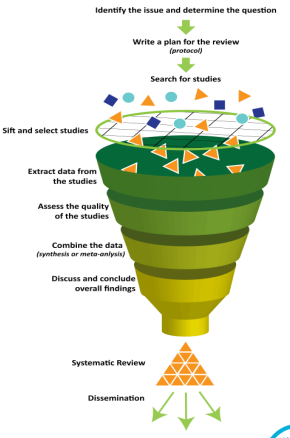
EuroHYP-1

Van der Worp et al. 2007

Need help?

Preclinical bodies of evidence

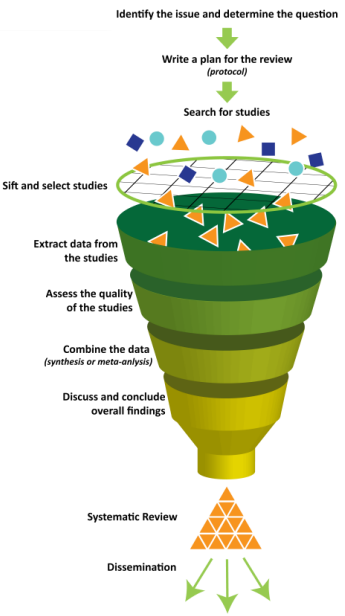
Search result	Included studies	ratio
310	58	1:5



Tools per phase

- Preclinical SR protocol format and Preclinical PROSPERO
- Step-by-step guide for searching
- Search filters for animal studies
- SyRF SR facility
- SYRCLE Risk of bias tool
- Guides to preclinical meta-analysis
- Evidence-Based Preclinical Medicine Journal
- … and more!

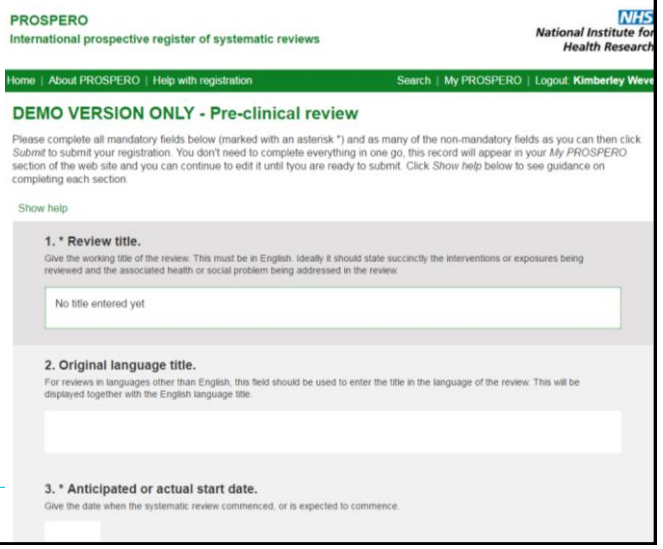
Accessible through www.syrcle.nl and/or www.camarades.info



Protocol registration in PROSPERO

Advantages:

- Prevent bias and selective reporting in the SR
- Structures the review process
- Prevents unnecessary duplication of SRs
- To be found soon at https://www.crd.york.ac.uk/PROSPERO/



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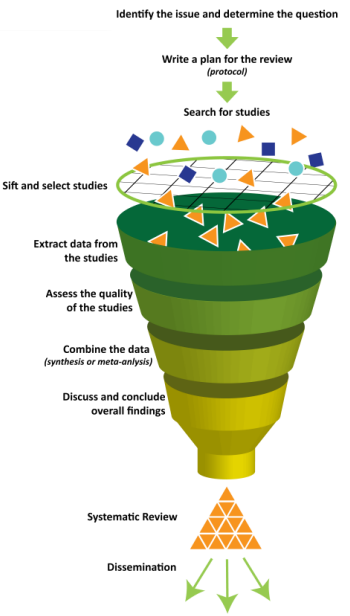
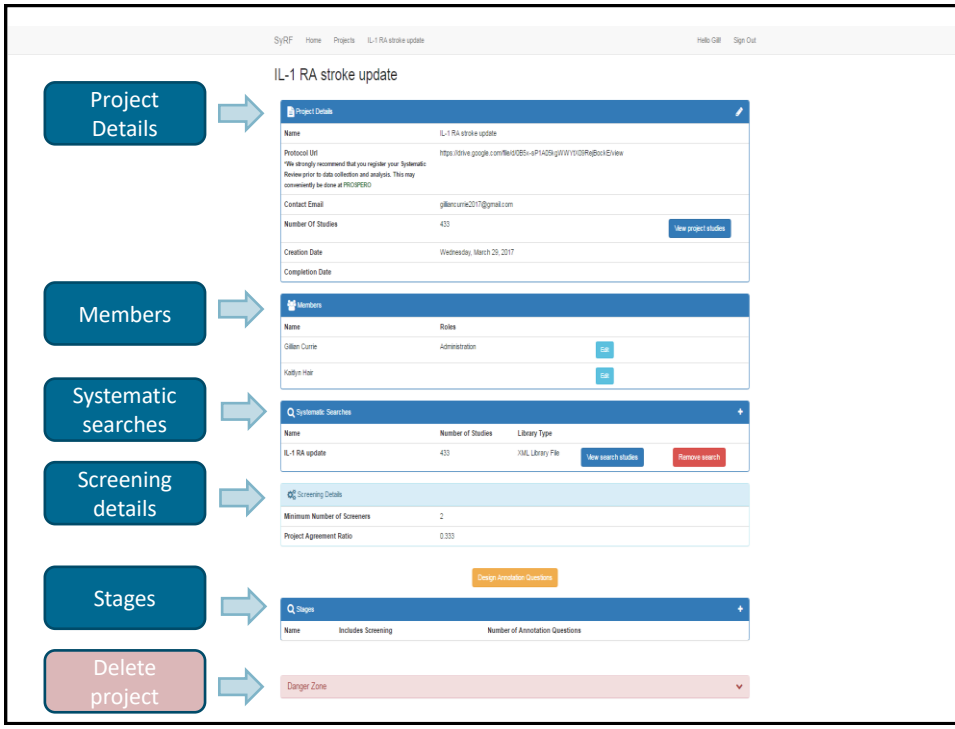


SyRF: screening, data extraction and MA

An easily accesible resource to aid systematic review and meta-analysis of *in vivo* studies.

Login

SYSTEMATIC
Review Facility




SyRF
Home
Projects
IL-1 RA stroke update
Hello Kaitlyn!
Sign Out
200 Screened
233 Remaining
Whole live animal models of ischaemic occlusive stoke of the middle cerebral or anterior cerebral arteries or their branches • Any primary study comparing treatment and control groups • Any mode of delivery of IL-1 RA (e.g. transgenic, viral, peripheral) at any time point and frequency • Infarct, neurobehavioural or mortality outcomes where the mean, variance and number of animals per group is reported or can be calculated • All languages
Models of haemorrhagic stroke, global ischaemia; in vitro studies • No control group, review, protocol paper, editorial
Excluded
Trimethyltin-evoked apoptosis of murine hippocampal granule neurons is accompanied by the expression of interleukin-1beta and interleukin-1 receptor antagonist in cells of ameboid phenotype, the majority of which are NG2-positive
A. Fledorowicz, I. Figiel, M. Zaremba, K. Dzwonek, R. Schliebs, B. Oderfeld-Nowak
Brain Research Bulletin, 2008
Abstract:
Interleukin-1beta (IL-1 beta) has been implicated in various neuropathologies, while IL-1 receptor antagonist (IL-1ra) has been shown to reduce neuronal injury. We investigated the pattern of expression of both cytokines in murine hippocampus after trimethyltin (TMT) intoxication. Using a ribonuclease protection assay, we demonstrated induction of transcription of IL-1 beta and IL-1ra 3 days following TMT treatment which correlated with the peak of neuronal apoptosis. At this time, immunocytochemical staining revealed enhanced expression of both cytokines in NG2 proteoglycan expressing ameboid cells located at the site of neurotoxic insult, some of which bound also the microglial marker, lectin. There was some overlap between NG2 and lectin staining. Our results suggest that the two cytokines are involved in apoptotic processes in dentate granule cells and indicate that the pro-apoptotic effect of IL-1 beta prevails over the presumed protective action of IL-1 ra. The novel finding of expression of both cytokines in NG2(+) cells of ameboid phenotype indicates that these cells, through the regulatory roles of pro- and anti-inflammatory cytokines, may be involved in control of neuronal death or survival after injury. (c) 2008 Elsevier Inc. All rights reserved.
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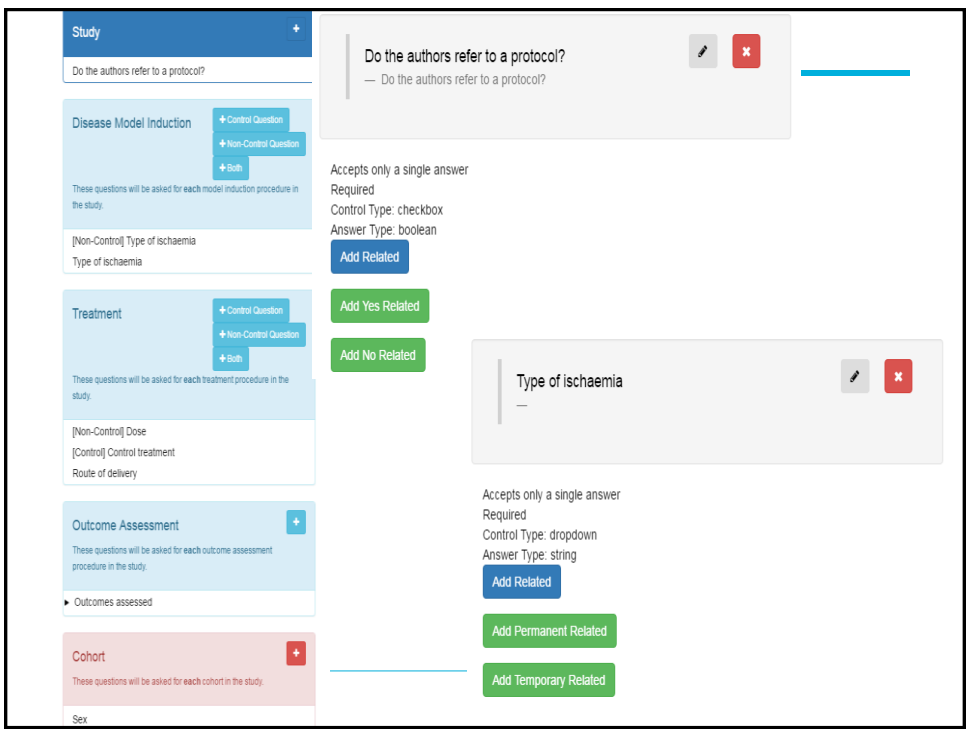
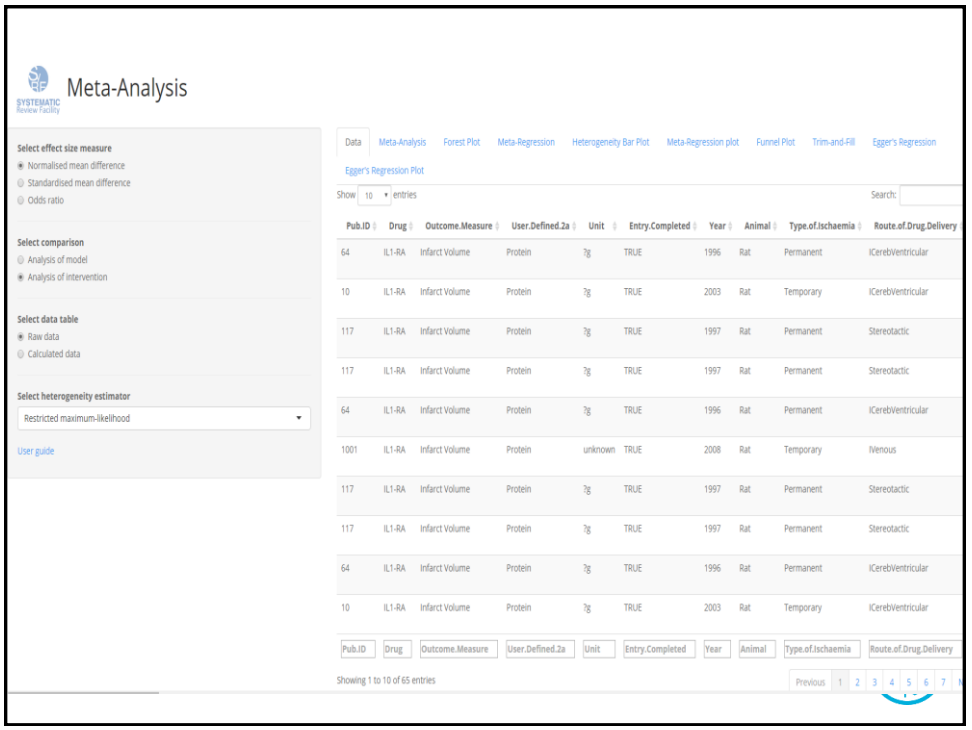
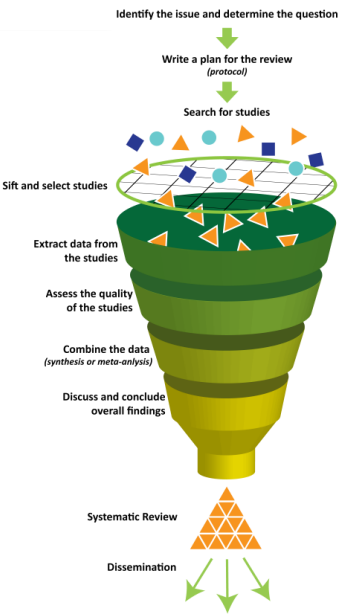

Study
Do the authors refer to a protocol?
Disease Model Induction
+ Control Question
+ Non-Control Question
+ Both
These questions will be asked for each model induction procedure in the study.
[Non-Control] Type of ischaemia
Type of ischaemia
Treatment
+ Control Question
+ Non-Control Question
+ Both
These questions will be asked for each treatment procedure in the study.
[Non-Control] Dose
[Control] Control treatment
Route of delivery
Outcome Assessment
These questions will be asked for each outcome assessment procedure in the study.
Outcomes assessed
Cohort
These questions will be asked for each cohort in the study.
Sex
Do the authors refer to a protocol?
— Do the authors refer to a protocol?
Accepts only a single answer
Required
Control Type: checkbox
Answer Type: boolean
Add Related
Add Yes Related
Add No Related
Type of ischaemia
—
Accepts only a single answer
Required
Control Type: dropdown
Answer Type: string
Add Related
Add Permanent Related
Add Temporary Related



Tools per phase

- Preclinical SR protocol format and Preclinical PROSPERO
- Step-by-step guide for searching
- Search filters for animal studies
- SyRF SR facility
- SYRCLE Risk of bias tool
- Guides to preclinical meta-analysis
- Evidence-Based Preclinical Medicine Journal
- … and more!

Accessible through www.syrcle.nl and/or www.camarades.info



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Thank you!


meta-analysis
systematic
review
animal
studies
bias
design
animals
clinical
SR
research
experimental
models
evidence
results
Hooijmans
validity
risk
new
intervention
data
quality
question
effect
measures
reporting