

The value of preclinical Systematic Reviews

Merel Ritskes-Hoitinga, DVM, PhD, Dipl. ECLAM
Prof. In Evidence-Based Laboratory Animal Science

SYRCLE

Department for Health Evidence

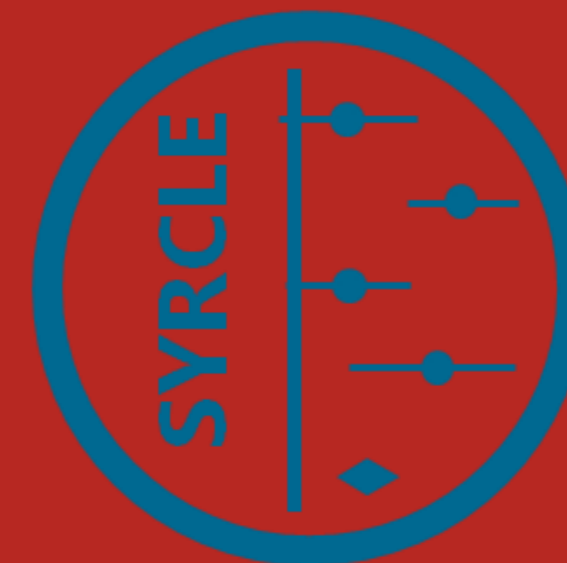
Radboudumc / Radboud University

The Netherlands

Merel.Ritskes-Hoitinga@radboudumc.nl



<https://www.youtube.com/embed/bpM60mTCZcM?rel=0&autoplay=1>



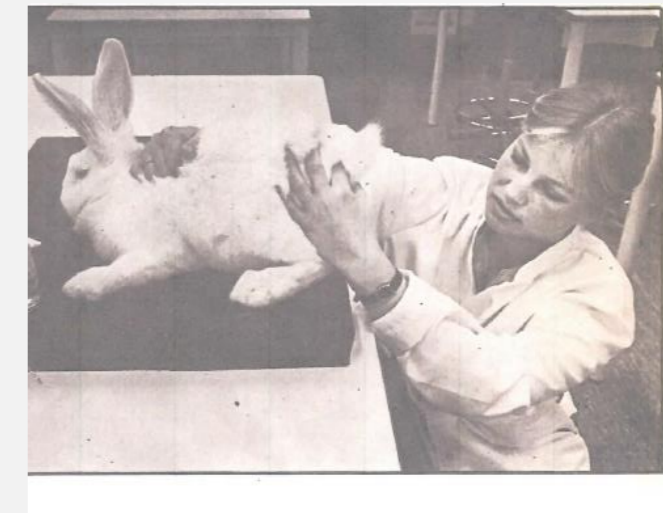
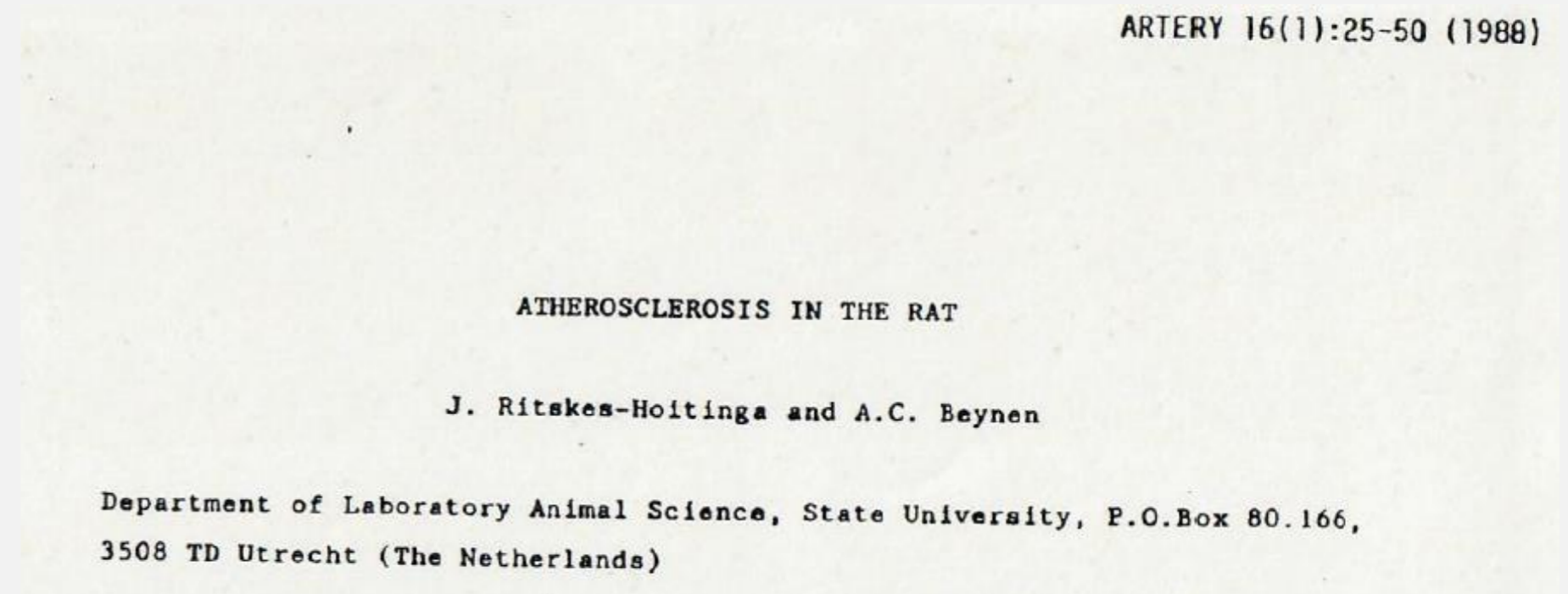
**SYstematic
Review
Center for
Laboratory (animal)
Experimentation**

www.syrcle.nl

Who am I?

- My full cv at www.ritskes-hoitinga.eu

- My "mission" arose when writing a literature review on "Atherosclerosis in the rat". Artery 16, 25-50, 1988.
- Achieving better science and better welfare and better translation simultaneously, and avoiding unnecessary animal studies



What are Systematic reviews?

Free e-learning

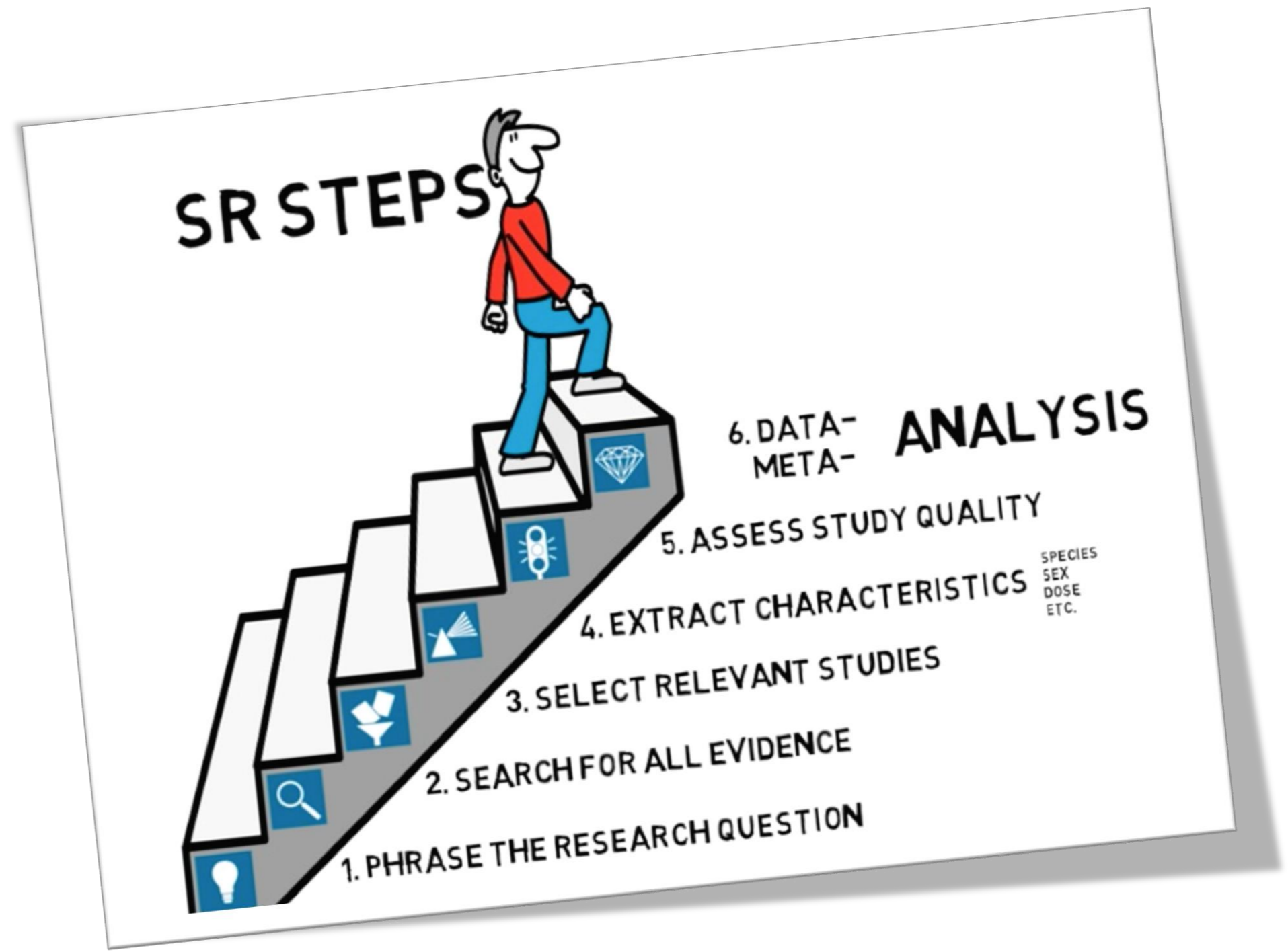
 Systematic Reviews of Animal Studies  



START 

<https://syrcl.eckphost.nl>
Registration code: syrcl

Radboudumc



>4000 participants from 65 countries

Cochrane Collaboration since 1993
SRs for human studies: Evidence-Based Medicine



**THE COCHRANE
COLLABORATION®**



Cochrane

Examples of benefits of preclinical SRs

- More evidence-based choice of (animal) models: De Vries RB, Tissue Engineering Part B 2012
- Phrase your research question precisely
- Transparency on quality of reporting
- Translational transparency: Cohen BMJ 2018
- Identifying relevant research questions - hypothesis generating: Hollyer 2018
- **Implementing 3Rs**, e.g. prevent unnecessary duplication: Yauw 2015
- Improving protection of humans in clinical studies: Horn 2001 and Pound 2004

**Choose model on the basis of evidence
instead of tradition.**

cartilage

bone



Osteochondral
lesion - rodent

Start with the human disease.

**Rodent is not a good model for studying
Tissue Engineering for cartilage
degeneration.**



Partial thickness
lesion - human

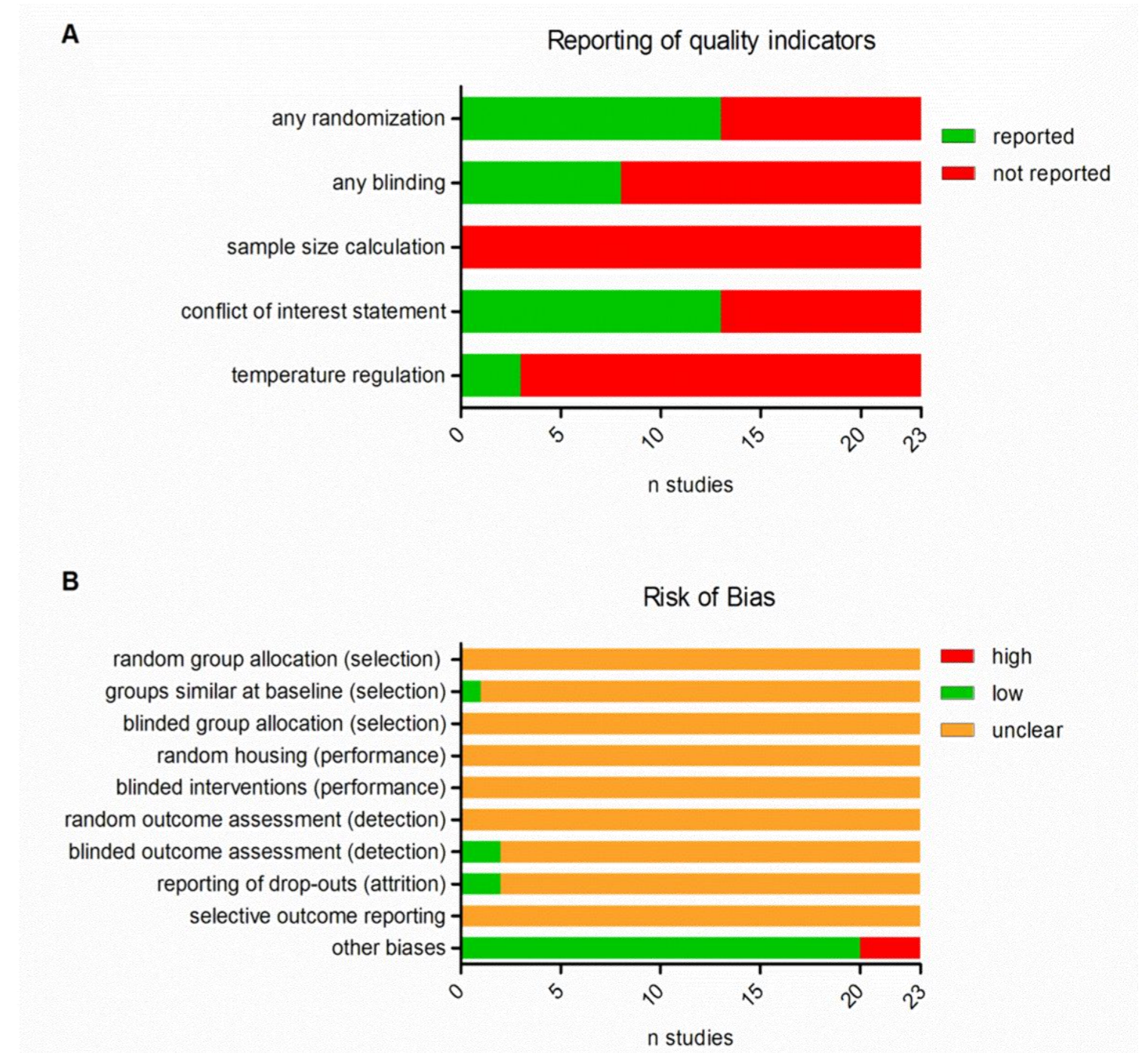
Phrase the research question precisely

Start with the human disease and ask patients what is important to them

The screenshot shows the homepage of the James Lind Alliance (JLA) website. The browser address bar shows the URL jla.nihr.ac.uk. A cookie consent banner is visible at the top. The main header features the JLA logo and the text "Priority Setting Partnerships". A navigation menu includes links for Home, About the JLA, The PSPs, Top 10s, JLA Guidebook, News and Publications, Making a difference, and Current surveys. The main content area is titled "The James Lind Alliance" and includes a brief description of the organization's mission. Below this, there are three featured sections: "The PSPs", "Top 10s", and "The JLA Guidebook". A "What's new" section highlights a recent update from October 2019. A "Mailing list" sign-up button is also present. A "JLA on Twitter" section shows a tweet from Katherine Cowan (@Katherine_JLA) regarding a survey on diabetes and pregnancy research. The Windows taskbar at the bottom shows the Start button, Chrome browser, and the system clock indicating 21:54 on 27-10-2019.

Transparency on quality of reporting – an unfortunate benefit...

50 – 80 % of publications lack essential details



Translational transparency A 'pick and mix approach' ...

INVESTIGATION

Oxford TB vaccine study calls into question selective use of animal data

Deborah Cohen *associate editor, The BMJ*

BMJ 2018;360:j5845 doi: 10.1136/bmj.j5845 (Published 10 January 2018)

Improving the conduct, reporting, and appraisal of animal research

All stakeholders must act decisively to fix endemic problems

Merel Ritskes-Hoitinga *professor*, Kim Wever *researcher*

SYRCLE, Department for Health Evidence, Radboudumc, Nijmegen, Netherlands

Hypothesis generating Fundamental neuroscience and systematic reviews also go together well

Journal of
Neurochemistry

JNC 

JOURNAL OF NEUROCHEMISTRY | 2019 | 148 | 712-730

doi: 10.1111/jnc.14633

ORIGINAL
ARTICLE



The evidence for the physiological effects of lactate on the cerebral microcirculation: a systematic review

Tristan R. Hollyer*[†] , Luca Bordoni[‡], Birgitte S. Kousholt^{†§} ,
Judith van Luijk[¶], Merel Ritskes-Hoitinga[¶] and Leif Østergaard*^{†**}

*Centre for Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus C, Denmark

[†]Institute for Clinical Medicine, Aarhus N, Denmark

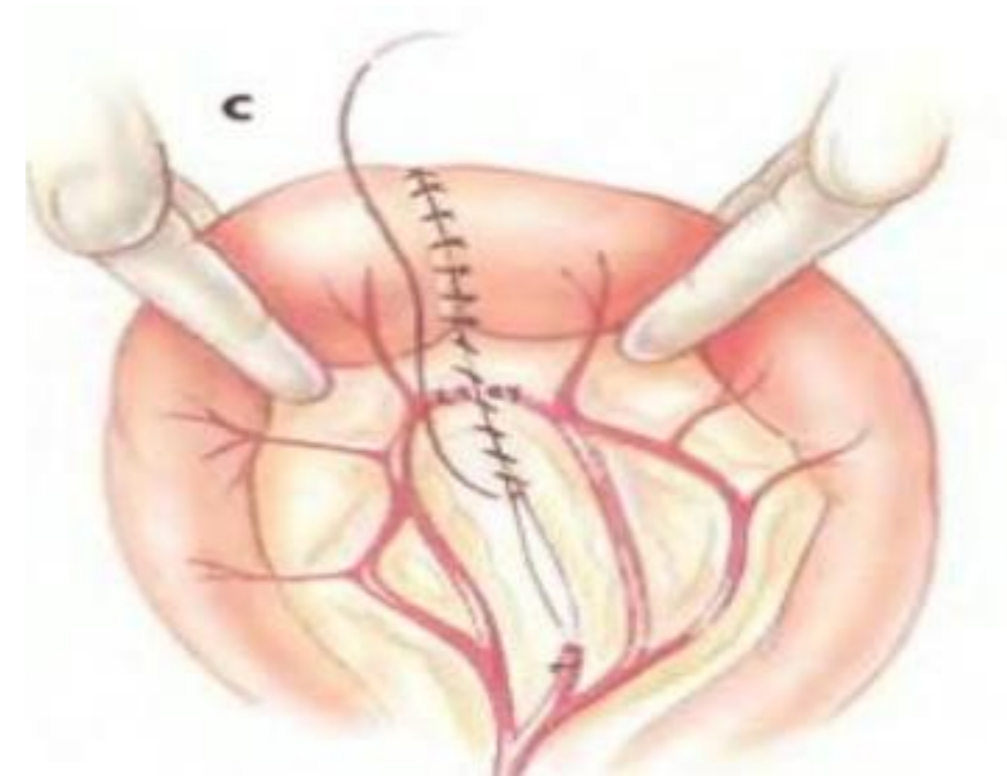
[‡]Department of Biomedicine South, Aarhus University, Aarhus C, Denmark

[§]Department of Clinical Medicine, AUGUST Centre, Aarhus University, Risskov, Denmark

[¶]SYstematic Review Centre for Laboratory Animal Experimentation (SYRCLE), Department for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands

**Department of Neuroradiology, Aarhus University Hospital, Aarhus C, Denmark

Systematic reviews make unnecessary repetition transparent



88 out of 1342 studies repeated

the adverse effect of chemotherapy on intestinal wound healing

Yauw, Wever, Br. J. Surgery 2015

Search filters for Pubmed and Embase at www.syracle.nl Lead to complete literature searches, preventing unnecessary duplication

Just copy -
paste!

SYRCLE's Pubmed search filter for animal studies.

("animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms:noexp] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms:noexp] OR "gorilla gorilla"[MeSH Terms] OR "pan paniscus"[MeSH Terms] OR "pan troglodytes"[MeSH Terms] OR "pongo pygmaeus"[MeSH Terms]) OR ((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR 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Protecting humans

Retrospective systematic review on preclinical evidence

Efficacy of Nimodipine in Stroke

Janneke Horn 2001

Retrospective systematic review on preclinical evidence

Safety and side-effects of anti-thrombotics in Stroke

Pandora Pound BMJ 2004

SR is one of the methods of syntheses of evidence



Conducting preclinical syntheses of evidence: the impact on research and researchers – a ZonMw case study

Julia Menon, Merel Ritskes-Hoitinga, Erica van Oort



Radboudumc



Ensuring Value in Research Funder Forum <https://sites.google.com/view/evir-funders-forum> Preclinical working group

Initial founders EVIR:

ZonMw (NL)
NIHR (UK)
PCORI (US)

10 guiding principles for funding

Principle 2:

Research should only be funded if set in the context of one or more existing **systematic reviews** of what is already known or an otherwise **robust** demonstration of a research gap.



The guiding principles of the
Ensuring Value in Research Funder's Forum
can also ensure value in preclinical research

M. Ritskes-Hoitinga¹, M. Westmore², D. Goble², K. Dunham³, E. Whitlock³, W. De Leeuw⁴, E. van Oort⁵, B. Van der Linden⁵

¹Radboud University Medical Center/SYRCLE, Nijmegen, The Netherlands

²National Institute for Health Research (NIHR) and University of Southampton, UK

³Patient-Centered Outcomes Research Institute (PCORI), USA

⁴University Medical Center Utrecht and Utrecht University, The Netherlands

⁵ZonMW, The Netherlands

Research questions and aims

What impacts does conducting preclinical systematic reviews have on researchers and (their) research?

A case study of SRs related to the ZonMw funded program of 8 years

ZonMW MKMD grant scheme

Identify potential impact

1

Funding + Workshop

- Funding (*enablement*)
- Workshops (*education + training*)



- Participants receive grant
- Participants follow the workshops

2

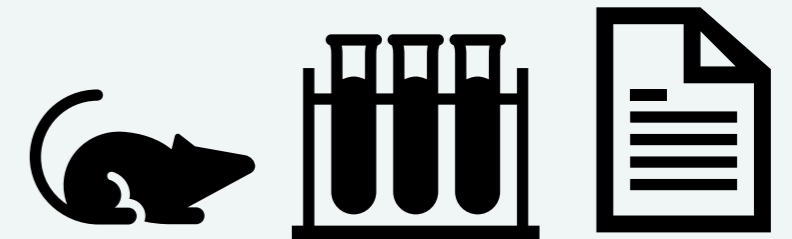
Coaching

- Coaching (*training + enablement*)

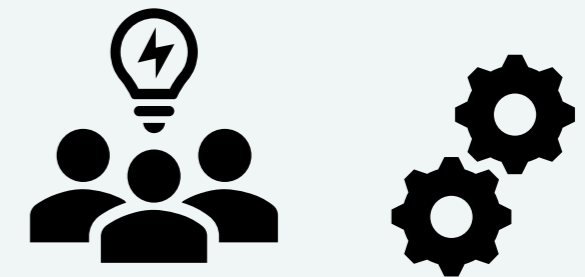


Participants perform Preclinical SRs

- Inventory
- Questionnaires
- Interviews



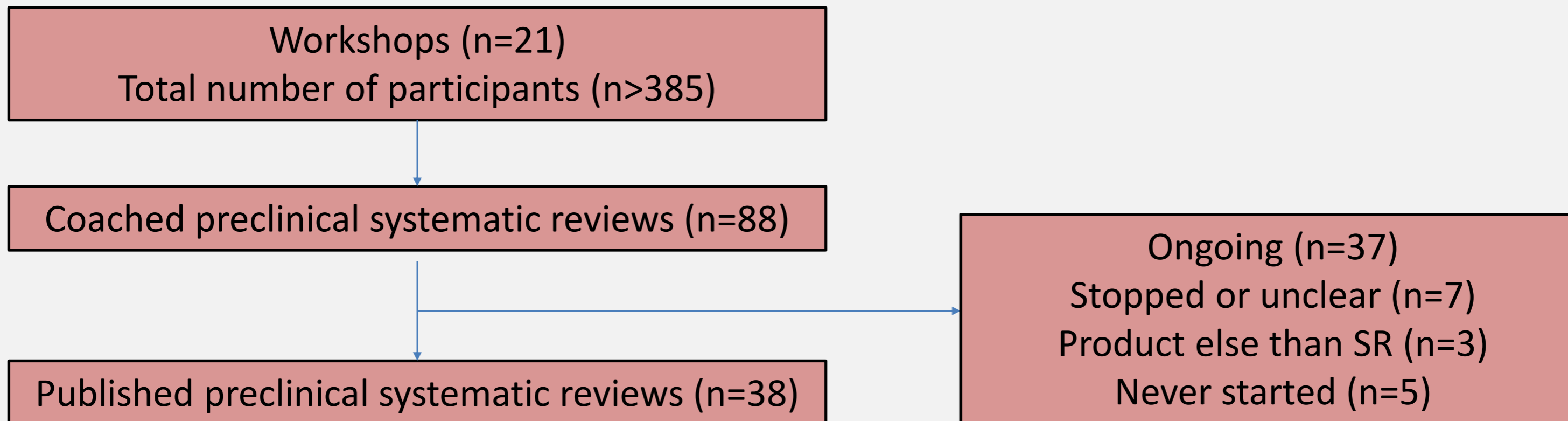
Impact on research ?



Impact on researchers ?

Results inventory

	2013	2014	2015	2016	2017	2019	2020	TOTAL
AVERAGE	8.4	8.5	8.0	9.0	8.3	7.8	8.1	8.2



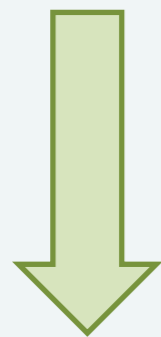
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MKMD grant scheme

Funding (*enablement*)
Workshops (*education + training*)
Coaching (*training + enablement*)



-Participants receive grant
-Participants follow the workshops



Participants perform Preclinical SRs

2

Opinion Change/Gain Insights

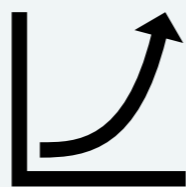
Impact on researchers: conduct of SRs make participants gain skills, insights, and realize some aspects of research



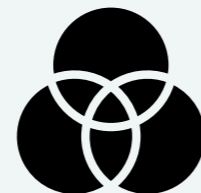
Confrontation with badly conducted/reported studies



Opinion change regarding animal research overall quality



Learn new skills
Understand value of SR



Gain insights on their field
(identify data gaps, bring new knowledge, confirm/refute theories)



Realize impact of research on animals
Realize own past mistakes

3

Impact on Research

Conduct of preclinical SRs seems to impact research at 3 levels



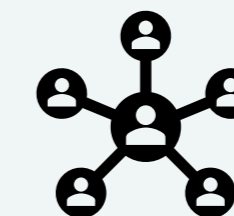
Impact at lab/team level

- Change how to plan, conduct, report experiments
- Knowledge transfer within team



Impact at field level

- Bring new insights, inspire new SRs and primary studies
- Opinion papers, advocate for change



Impact at a science community level

- Make SRs a requirement for ethical/funders application
- Increase training/education

Conclusion & Future directions ZonMw impact study

- Conducting preclinical SRs impact research and researchers by influencing thinking, behaviour and actions – full report:

https://www.zonmw.nl/fileadmin/zonmw/documenten/Fundamenteel/MKMD_2020/Report_ZonMw_Preclinical_impact_study_SR_final.pdf

- Future directions:
 - The ZonMw program was praised and appreciated by the participants
 - Advisable for much broader use

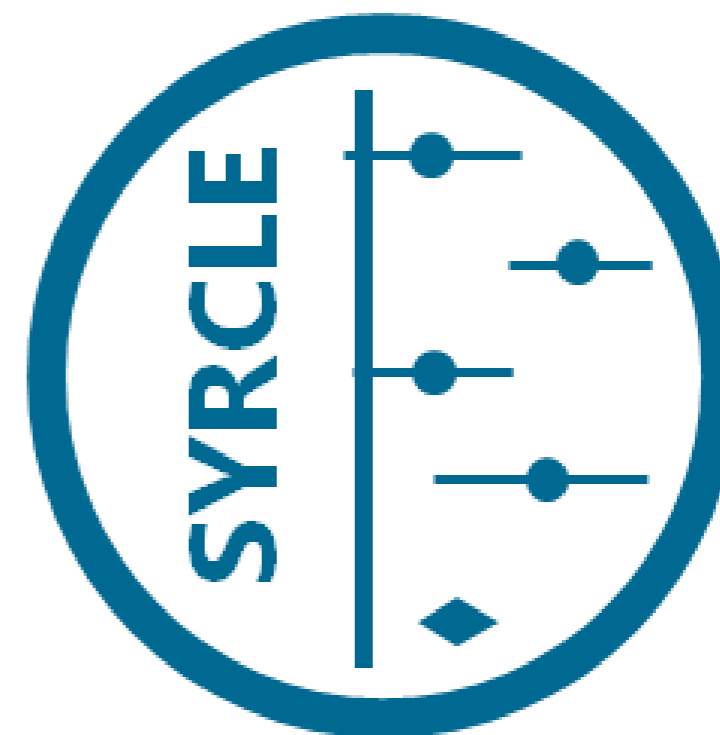
Take home messages and future considerations

- SRs show many benefits / impact on research
- The execution of SRs shows many impacts on thinking and behaviour / impacts on researchers
- For the sake of animals and humans and science it is necessary to conduct SRs before embarking on new projects
- Funders can play a major role in stimulating SRs by funding education and coaching and execution

Thank you for listening.

More information:

- Website www.syracle.nl
 - *Free newsletters*
 - *E-learning*
 - *Workshops*
 - *Coaching*
 - *Guidelines and tools*
- Contact: Merel.Ritskes-Hoitinga@radboudumc.nl



Questions?