

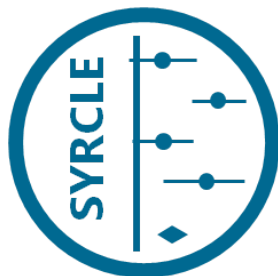
# Systematic Reviews and Meta-analysis of preclinical (animal) studies

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Department for Health Evidence, Radboud university medical center

19 Febr 2019 Federal Ministry of Education and Research, Berlin



SYstematic  
ReView  
Centre for  
Laboratory animal  
Experimentation

Radboudumc

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# Once upon a time....

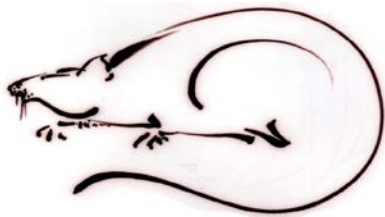
## My first literature review

ARTERY 16(1):25-50 (1988)

ATHEROSCLEROSIS IN THE RAT

J. Ritskes-Hoitinga and A.C. Beynen

Department of Laboratory Animal Science, State University, P.O.Box 80.166,  
3508 TD Utrecht (The Netherlands)

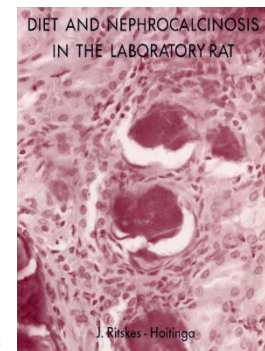


ARTERY 16(1):25-50 (1988)

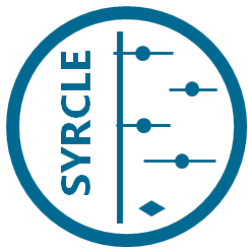
### ATHEROSCLEROSIS IN THE RAT

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Universiteit Utrecht



**3R** Research Centre  
Refine Reduce Replace



**Radboudumc**  
university medical center



SYDDANSK UNIVERSITET  
UNIVERSITY OF SOUTHERN DENMARK



**Radboudumc**

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3R → SR

**THE NEXT  
STEPS  
TOWARDS  
RESPONSIBLE  
ANIMAL-BASED  
RESEARCH**

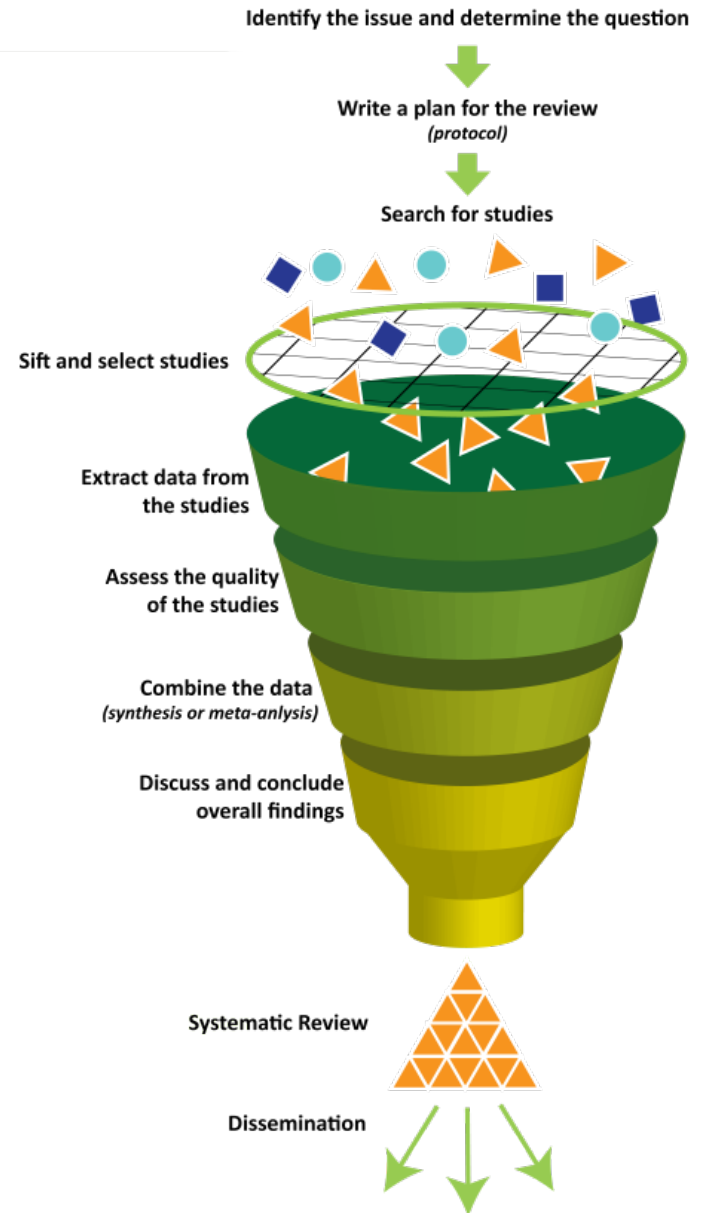
EVALUATION OF STRATEGIES TO IMPROVE SCIENTIFIC QUALITY AND  
RESPONSIBLE ANIMAL USE IN RESEARCH



Judith van Luijk

# Definitions

- **Systematic Review (SR):**
  - The process of systematically locating, appraising and synthesizing evidence from scientific studies in order to obtain a reliable overview.
- **Meta-analysis (MA) (optional):**
  - Combination of results of individual studies in an overall statistical analysis



# Systematic reviews



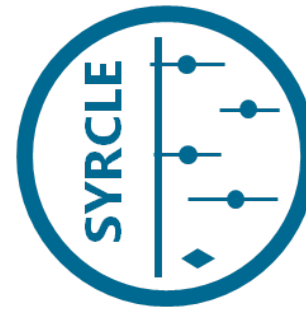


**THE COCHRANE  
COLLABORATION®**

**SRs in Evidence-Based  
Medicine =  
routine since 1992**



**Cochrane**



Systematic  
Review  
Centre for  
Laboratory animal  
Experimentation



# SYRCLE activities

- Workshops



- Coaching

Reinier Post

- E-learning



- Execution



- Tools and guidelines

- [www.syracle.nl](http://www.syracle.nl)



# E-learning



Systematic Reviews of Animal Studies



**START** ▶

<https://syrcle.ekphost.nl>  
Registration code: syrcle

Radboudumc



Ministry of Economic Affairs  
of the Netherlands



- Lack of knowledge of concept and advantages SRs
- High-quality SRs require the involvement of experts with methodological knowledge and skills
- ZonMw program requires hiring SYRCLE for workshops and coaching to guarantee quality

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# *One-day workshops*

- Goals
  - thoroughly familiar with concept and steps
  - Get basic skills to start own SR with coaching
- Maximum of 20 participants – 2 SYRCLE trainers
- Both in the Netherlands and abroad: Belgium, Norway, Denmark, Sweden, Switzerland (tour), Germany, UK, Spain, Italy, Brazil
- good combination of theory and practical exercises



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# Coaching

- Partly education, partly research
- SR process too complex for participants to be able to conduct SR independently after workshop/course
- We support and provide feedback on all steps of the SR: from protocol to manuscript. Tools and guidelines available
- On average 40-50 hours coaching per SR
- SR completion takes 3 months to 2 years; results in good publications, cited well

www.nature.com/scientificreports  
SCIENTIFIC REPORTS

OPEN A combined pre-clinical meta-analysis and randomized confirmatory trial approach to improve data validity for therapeutic target validation

Received: 08 February 2015  
Accepted: 22 July 2015  
Published: 27 August 2015

Pamela WM Kleikers<sup>1,2</sup>, Carlijn Hooijmans<sup>1,2</sup>, Eva Göbbel<sup>3</sup>, Friederike Langhauser<sup>1</sup>, Sarah SJ Rewell<sup>4</sup>, Kim Rademacher<sup>1</sup>, Merel Rittkes-Hoitinga<sup>1</sup>, David W Howells<sup>5</sup>, Christoph Kleinschnittz<sup>2,6</sup> & Harald HHW Schmidt<sup>1,2</sup>

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# Output until November 2018

Project	Nrs. SR started	Nrs. completed
ZonMw I	31	26
ZonMw II	24	2
Reinier Post	10	2
Other	3	2
SYRCLE	15	10

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# Citations (Web of Science Feb '19)

- Wever KE, PloSOne 2012 94
- Hooijmans CR J Alzheimers disease 2012 72
- SYRCLE's Risk of Bias tool 221

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# Benefits of preclinical SRs



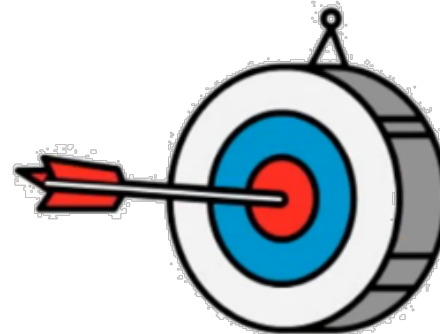
PROVIDE OVERVIEW OF AVAILABLE EVIDENCE

IDENTIFY KNOWLEDGE GAPS

CRITICAL APPRAISAL OF STUDY QUALITY

IDENTIFY FACTORS INFLUENCING TREATMENT EFFICACY

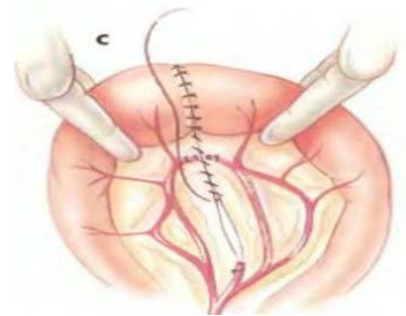
INFORM EXPERIMENTAL DESIGN OF ANIMAL CLINICAL STUDIES



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# Intestinal anastomosis models

- 350 publications
  - 1300 studies
  - 73304 animals used
- 
- 83 % no mention of sterility in surgery
  - 91% no mention of postoperative analgesia



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# 1342 studies – Reduction possible

Unnecessary repetition

88 studies on adverse effects of chemotherapy on wound healing

42 studies on fibrin glue

18 studies on the use of growth hormone

# SR also for basic science



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

Journal:	<i>Journal of Neurochemistry</i>
Manuscript ID	JNC-2018-0476.R3
Manuscript Type:	Original Article
Date Submitted by the Author:	18-Nov-2018
Complete List of Authors:	Hollyer, Tristan; Aarhus Universitet, CFIN; Aarhus Universitet, Institute of Clinical Medicine Bordoni, Luca; Aarhus Universitet, Department of Biomedicine Kousholt, Birgitte; Aarhus Universitet, Institute for Clinical Medicine; Aarhus Universitet, AUGUST Centre Østergaard, Leif; Aarhus Universitet Health, Center of Functionally Integrative Neuroscience and MINDLab; Aarhus Universitetshospital, van Luijk, Judith; Radboud University Medical Center, SYRCLE Ritskes-Hoitinga, Merel; Radboud University Medical Centre, SYRCLE
Area/Section:	Bioenergetics & Metabolism
Keywords:	systematic review, lactate, microcirculation, cerebral blood flow, brain

SCHOLARONE™  
Manuscripts



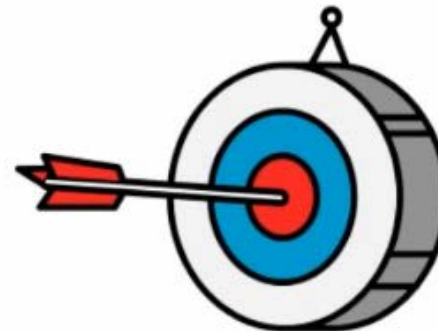
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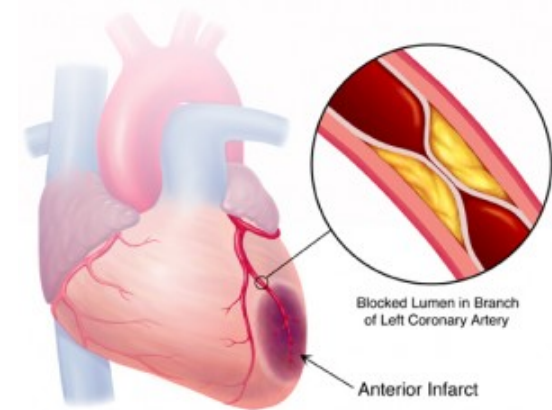
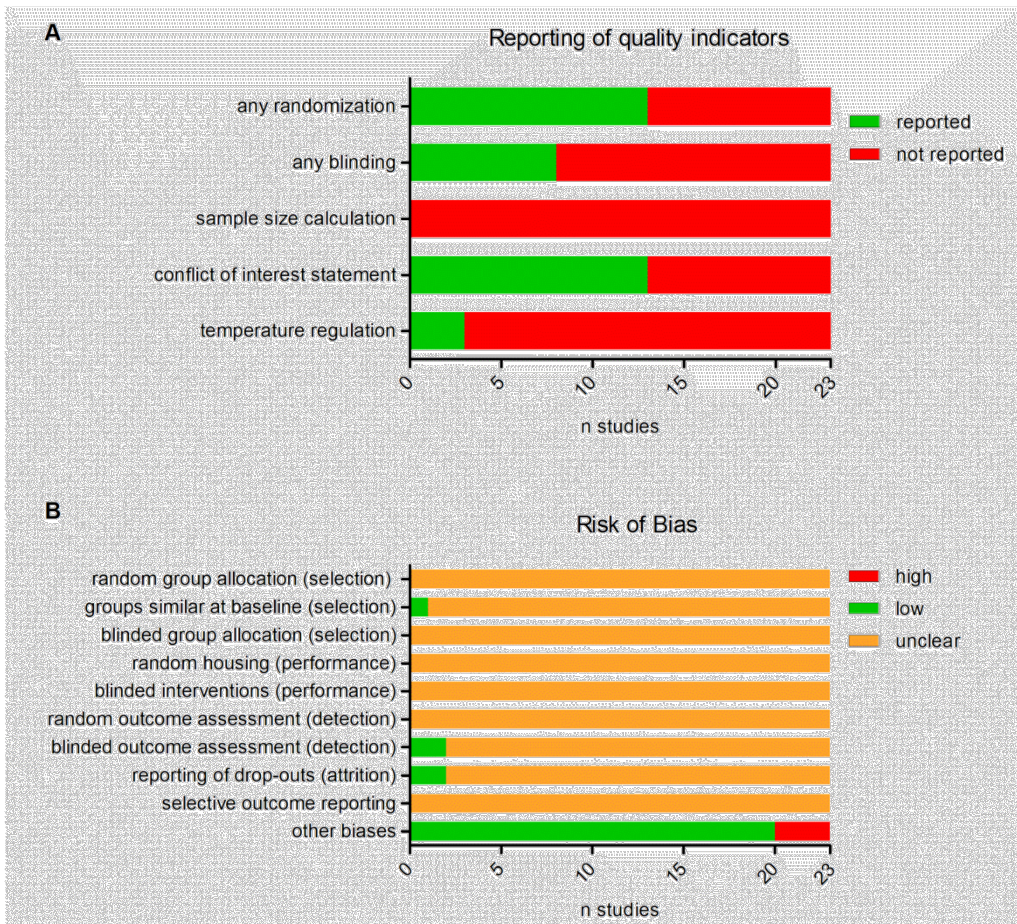
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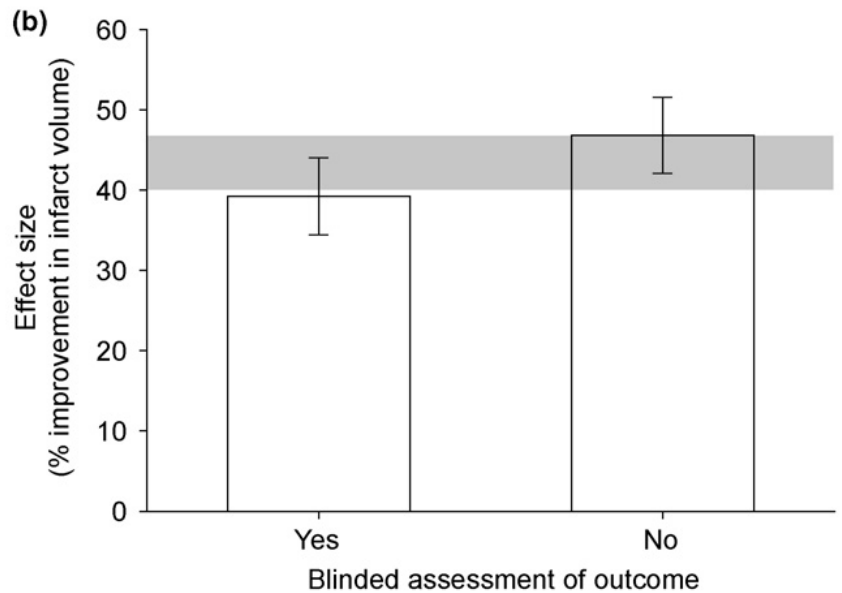
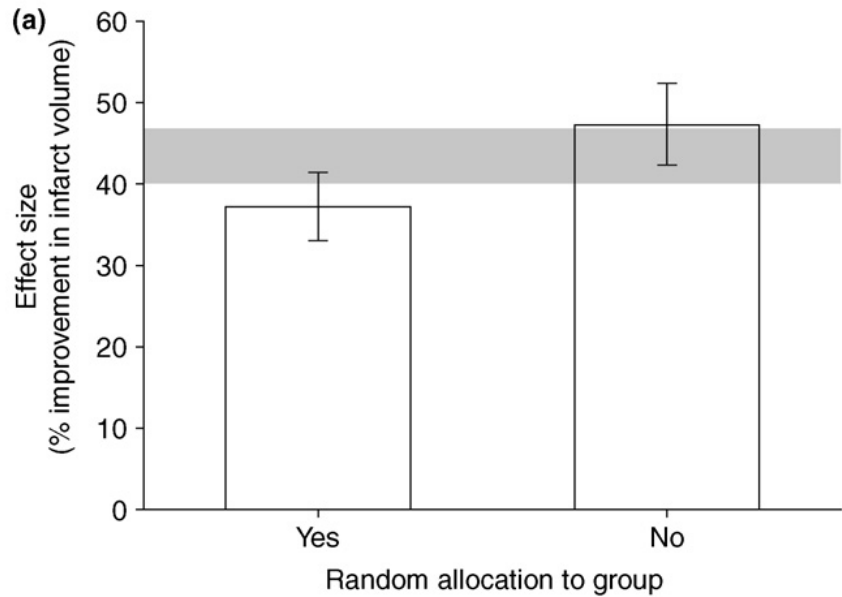


# Study quality



A. Poor reporting  
B. Unclear risks of bias

Hesen, ....Wever et al. PloSOne 2017– metformin in Myocardial Infarcts



**overestimation  
of effect size  
'optimism bias'**



**no randomization  
no blinding**



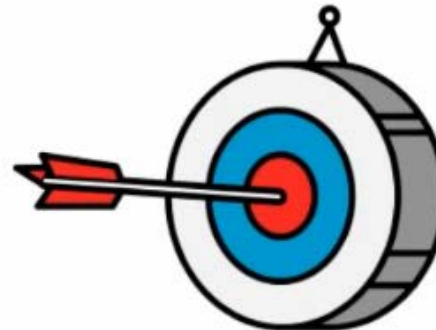
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INFORM EXPERIMENTAL DESIGN OF **ANIMAL** **CLINICAL** STUDIES



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# **Inform experimental design: Evidence-based choice of animal models**

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# Evidence-based choice of animal models

- The importance of rat strain when studying physiology of vascular function during pregnancy / eclampsia.
  - van Drongelen, Am J Physiol Heart Circ Physiol. 2012, 303, H639



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# Evidence-based choice of animal models

The importance of **large** animal models in tissue engineering research for bladder and urological medical problems

- Sloff M, PloSOne 2012 – SR on urinary diversion
- Sloff M, J. Urology 2014 – SR on bladder TE

The importance of large animal models in tissue engineering for cartilage defects:

- De Vries RB, Tissue Engineering Part B 2012

Choice of models for inflammatory bowel disease:

- Zeeff SB, Inflammatory Bowel Dis 2016

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**Inform clinical trial design**

**translation to humans**

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# **Efficacy**

## **Nimodipine for Stroke**

### **Janneke Horn 2001**

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# Side-effects

## Thrombolytics for Stroke

### Pandora Pound 2004

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# ENABLE trial

- Positive results from animal models of heart failure (HF) did not translate to clinic (Cowburn Eur Heart J 2001)
- Therapy gave early risk of worsening heart failure, due to fluid retention in humans (Kalra Int J Cardiol 2002)
- SR of 9 animal studies on HF showed no significant benefit or harm (DS Lee J Cardiac Failure 2003)

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~4 / 1000

# Stroke and MS



Collaborative Approach to Meta Analysis and

•C•A•M•A•R•A•D•E•S•

Review of Animal Data from Experimental Studies

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# Propatria trial Netherlands

## PRObiotics in PANcreatitis TRIAL

- Probiotic: Ecologic 641
  - Administration: twice daily for 28 days in jejunum
  - Mortality significantly higher in experimental group (16% vs 6%)
- 
- What were the results of the animal studies??



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# Propatria trial

## Systematic reviews of animal studies

- Major differences in experimental design compared to the human trial
  - Type of probiotics
  - Timing of administration
  - Route of administration
  - Acute pancreatitis induction

**Was it safe to start a clinical trial?**

**How are animal data analysed when planning clinical trials?**



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

Researchers were disappointed when a clinical trial of a new tuberculosis vaccine failed to show benefit, but should it have gone ahead when animal studies had already raised doubts and what does it mean for future research? **Deborah Cohen** investigates

Deborah Cohen *associate editor, The BMJ*

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## 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



BMJ 2018;360:k124 doi: 10.1136/bmj.k124 (Published 11 January 2018)

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**EDITOR'S CHOICE**

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**We need better animal research, better reported**

Fiona Godlee *editor in chief*

The BMJ

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# TB Booster vaccination MVA85A

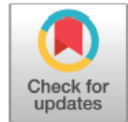
- Trial in children in South Africa did not result in a positive effect of the booster vaccination for tuberculosis (TB)
- A SR of animal studies revealed afterwards that also animal studies did not demonstrate a favourable effect (Kashangura R Int J Epidemiol 2015)
- A **'pick and mix approach' of animal studies** was applied for obtaining ethical approval for the clinical trial and for obtaining funding. E.g. a primate study with high mortality in the booster group, was omitted from the results

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# Strider trial

BMJ 2018;362:k4007 doi: 10.1136/bmj.k4007 (Published 25 September 2018)

Page 1 of 1



## LETTERS

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### STOPPING OF VIAGRA TRIAL

## Comprehensive literature search for animal studies may have saved STRIDER trial

Michael E Symonds *professor*, Helen Budge *professor*

Early Life Research Unit, Division of Child Health, Obstetrics and Gynaecology, Nottingham Digestive Disease Centre and Biomedical Research Centre, School of Medicine, University of Nottingham, Nottingham NG7 2UH, UK

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# Investigator brochures (IB) lack important information on animal studies

Wieschowski PloSBiol 2018:

- 109 recent IB's with 708 preclinical efficacy studies
- 89% not published / peer-reviewed
- Reporting of sample size in 26%, 0% blinding, 4% randomization, 27% gave experimental specifications
- 82% of IB's only reported studies with positive effects
- Most IB's did **not** allow a systematic appraisal of the strength of supporting preclinical findings

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# Investigator brochures (IB) lack important information on animal studies

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SR CAN REALLY HELP

- 89% not published, peer-reviewed

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# Ensuring Value in Research Funder Forum

## ZONMW (NL) NIHR (UK) PCORI (US)

### 10 guiding principles for funders

<https://sites.google.com/view/evir-funders-forum/guiding-principles>

#### 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.

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# Poster on Funder Forum guiding principles for preclinical research

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

**M. Ritskes-Hoitinga<sup>1</sup>, M. Westmore<sup>2</sup>, D. Goble<sup>2</sup>, K. Dunham<sup>3</sup>, E. Whitlock<sup>3</sup>, W. De Leeuw<sup>4</sup>, E. van Oort<sup>5</sup>, B. Van der Linden<sup>5</sup>**

<sup>1</sup>Radboud University Medical Center/SYRCLE, Nijmegen, The Netherlands

<sup>2</sup>National Institute for Health Research (NIHR) and University of Southampton, UK

<sup>3</sup>Patient-Centered Outcomes Research Institute (PCORI), USA

<sup>4</sup>University Medical Center Utrecht and Utrecht University, The Netherlands

<sup>5</sup>ZonMW, The Netherlands

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# Take home message on SRs

- Evidence-based science
- Transparency on quality of reporting
- Translational transparency
  
- Identifying relevant research questions
- Implementing 3Rs, e.g. prevent unnecessary duplication
- Improving project planning of animal and human studies



# More information:



- Website [www.syracle.nl](http://www.syracle.nl)
  - *Free newsletters*
  - *E-learning*
  - *Workshops*
  - *Coaching*
- Contact: [Merel.Ritskes-Hoitinga@radboudumc.nl](mailto:Merel.Ritskes-Hoitinga@radboudumc.nl)

