The role of systematic reviews in improving the internal validity and reporting quality of animal research

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Systematic reviews in animal research: Launch of the CAMARADES-NC3Rs Systematic Review Facility (SyRF)

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Pioneering Better Science

A driver to improve research practices

Systematic reviews have been instrumental in raising the standards of clinical research

Shine a light on current practices

Provide evidence of their impact on experimental results

Systematic reviews are a driver to :

- Improve internal validity
- Improve reporting quality
- Reduce publication and reporting bias

A driver to improve research practices

BIAS IN TREATMENT ASSIGNMENT IN CONTROLLED CLINICAL TRIALS

THOMAS C. CHALMERS, M.D., PAUL CELANO, M.D., HENRY S. SACKS, PH.D., M.D., AND HARRY SMITH, JR., PH.D.

Abstract Controlled clinical trials of the treatment of acute myocardial infarction offer a unique opportunity for the study of the potential influence on outcome of bias in treatment assignment. A group of 145 papers was divided into those in which the randomization process was blinded (57 papers), those in which it may have been unblinded (45 papers), and those in which the controls were selected by a nonrandom process (43 papers). At least one prognostic variable was maldistributed ($P<0.05$) in 14.0 per cent of the blinded-randomization studies, in 26.7 per cent of the unblinded-randomization studies, and in 58.1 per cent of the nonrandomized studies. Differences in case-fatality rates between treatment and control groups ($P<0.05$) were found in 8.8 per cent of the blinded-randomization studies, 24.4 per cent of the unblinded-randomization studies, and 58.1 per cent of the nonrandomized studies. These data emphasize the importance of keeping those who recruit patients for clinical trials from suspecting which treatment will be assigned to the patient under consideration. (N Engl J Med 1983; 309:1358-61.)

Clinical trials of treatment for acute myocardial infarction
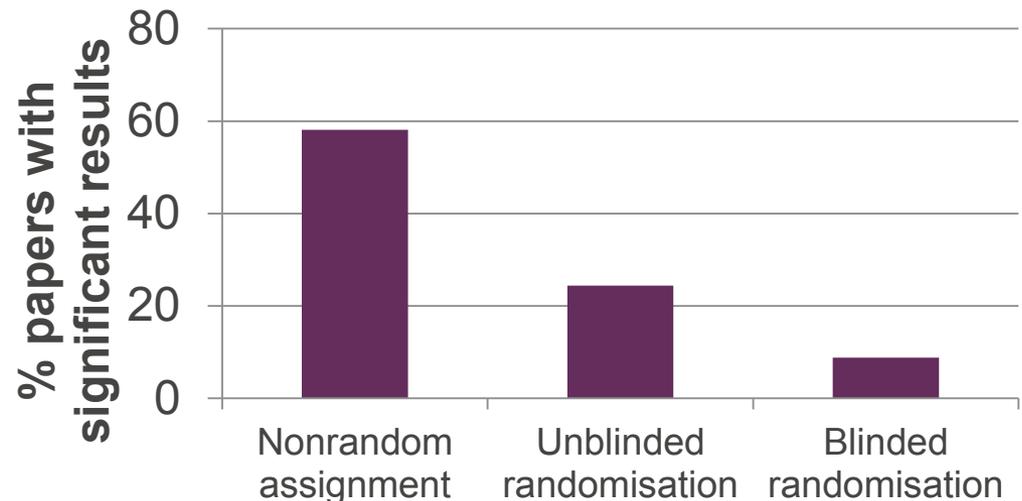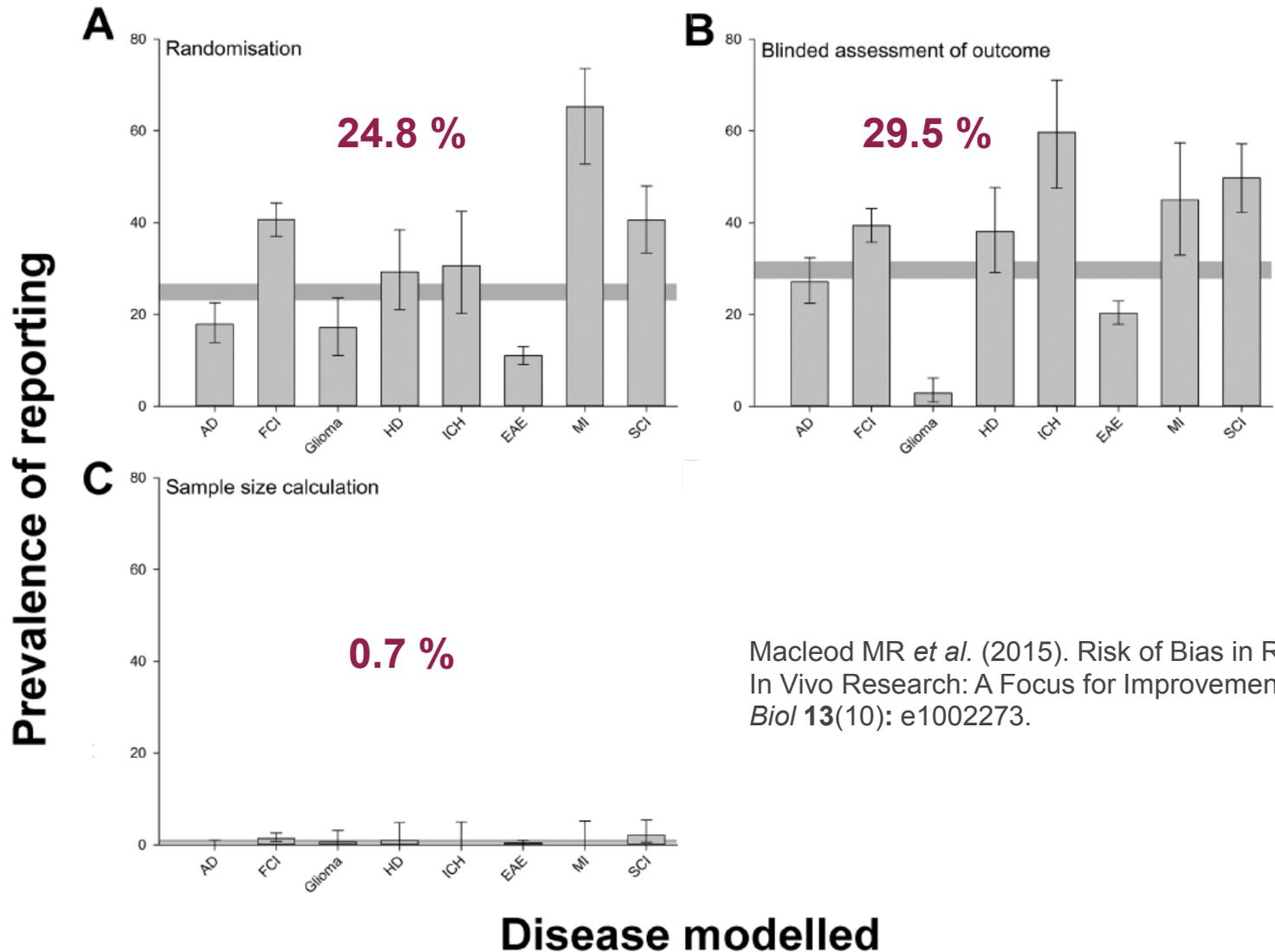
Internal validity

Risk of bias assessed as part of the systematic review

Measures used to reduce validity threats include:

- Random allocation to treatment groups
- Allocation concealment
- Blinding during outcome assessment
- Sample size determined by power calculation
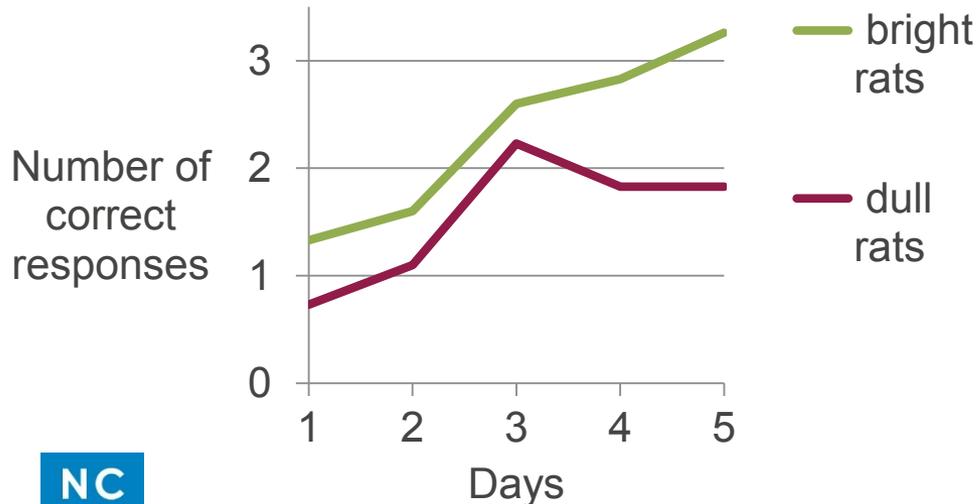- Inclusion/exclusion criteria

Internal validity – scale of the problem

Macleod MR *et al.* (2015). Risk of Bias in Reports of In Vivo Research: A Focus for Improvement. *PLoS Biol* **13**(10)**:** e1002273.

Internal validity – blinding

- 12 students

- Maze-bright and maze-dull rats

- Elevated T-maze, dark arm reinforced

- Rats had been labelled bright or dull <u>randomly</u>

- Only difference was in the minds of the investigators!

Rosenthal R, Fode KL (1963). The effect of experimenter bias on the performance of the albino rat. *Behavioral Science* **8**(3)**:** 183-189.

Internal validity – blinding

- Animal models of multiple sclerosis

- Comparison of blinded and non-blinded studies

Non-blinded studies
Effect size = **41%**

Blinded studies
Effect size = **30%**

Studies not blinded **overestimate** treatment efficacy

Vesterinen HM *et al*. (2010) Improving the translational hit of experimental treatments in multiple sclerosis. Mult Scler;16:1044-55.
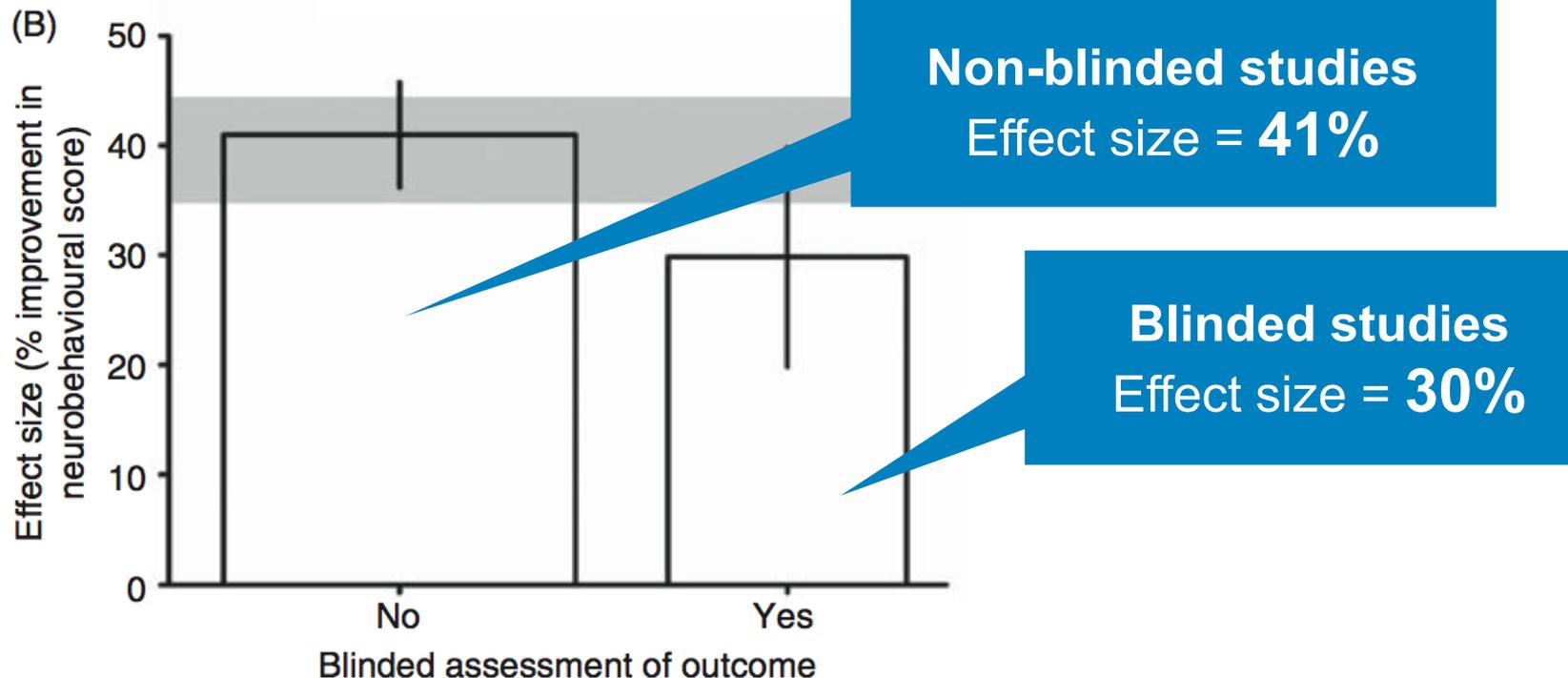
Internal validity – blinding
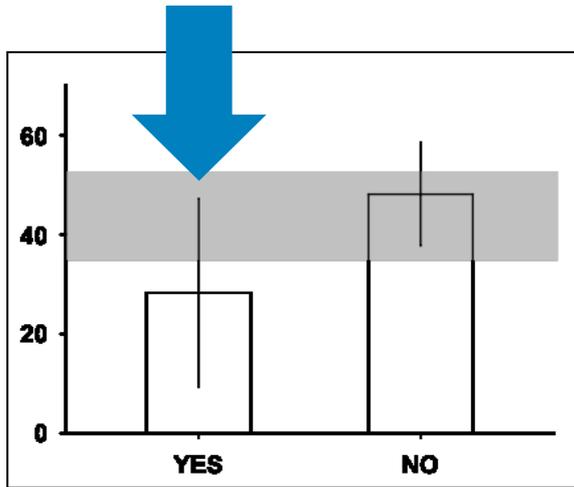
Stroke
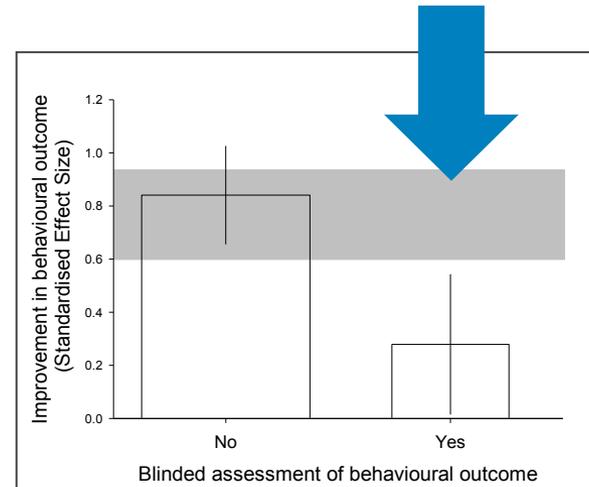
Alzheimer's disease

All data from:

Collaborative Approach to Meta Analysis and
·C·A·M·A·R·A·D·E·S·
Review of Animal Data from Experimental Studies
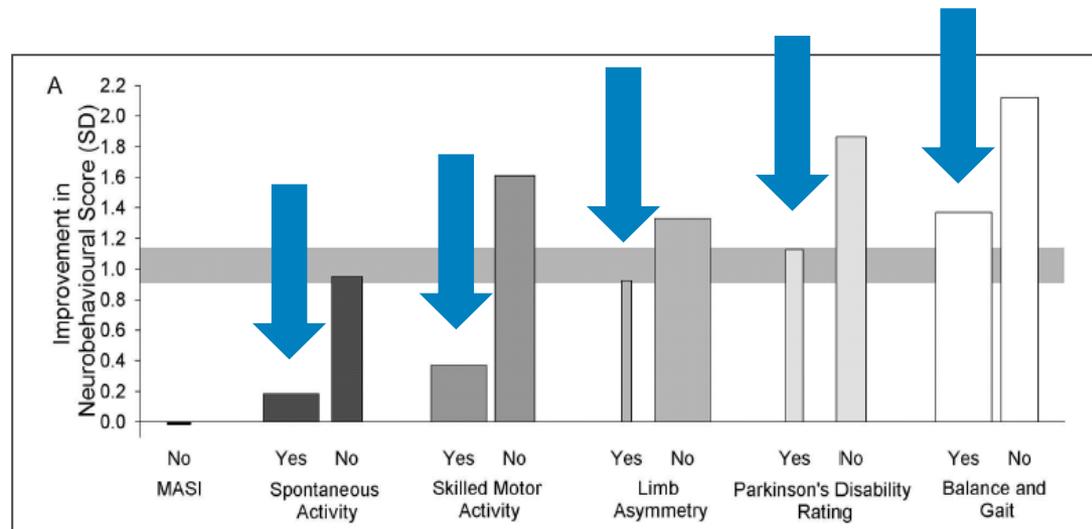
Parkinson's disease

Internal validity – randomisation

Method is important – haphazard is not random

Use a validated procedure (e.g. computer generated, throw a dice, flip a coin)

Randomisation is crucial for two reasons:

1. Minimise selection bias

e.g. haphazard selection may results in slowest mice allocated to the same group

2. Key assumption of the statistical analysis

Different groups should be drawn from the same background population using random sampling

Internal validity – randomisation

- Animal models of multiple sclerosis

- Comparison of randomised and non-randomised studies

Non-randomised studies
Effect size = **42%**

Randomised studies
Effect size = **21%**

Studies not randomised **overestimate** treatment efficacy

Vesterinen HM *et al*. (2010) Improving the translational hit of experimental treatments in multiple sclerosis. Mult Scler;16:1044-55.

Internal validity

IL-1RA in animal models of stroke

Categories (x-axis): Random allocation to groups, Blinded induction of ischeamia, Blinded assessment of outcome, Sample size calculation

Legend: 2009, 2016

McCann SK, Cramond F, Macleod MR, Sena ES (2016). Systematic Review and Meta-Analysis of the Efficacy of Interleukin-1 Receptor Antagonist in Animal Models of Stroke: an Update. *Translational stroke research* **7**(5)**:** 395-406.

Internal validity

IL-1RA in animal models of stroke

"The 2009 systematic review highlighted areas of weakness with respect the lack of reporting on certain aspects of experimental design. While we did not necessarily agree with all recommendations and also felt that not-reported did not mean not done we did take on board that future studies did need to more fully report details of experimental design. This change is reflected in the positive outcome of the follow-up 2016 systematic review"

--- Professor Stuart Allan, University of Manchester

Random allocation to groups | Blinded induction of ischeamia | Blinded assessment of outcome | Sample size calculation

McCann SK, Cramond F, Macleod MR, Sena ES (2016). Systematic Review and Meta-Analysis of the Efficacy of Interleukin-1 Receptor Antagonist in Animal Models of Stroke: an Update. *Translational stroke research* **7**(5)**:** 395-406.
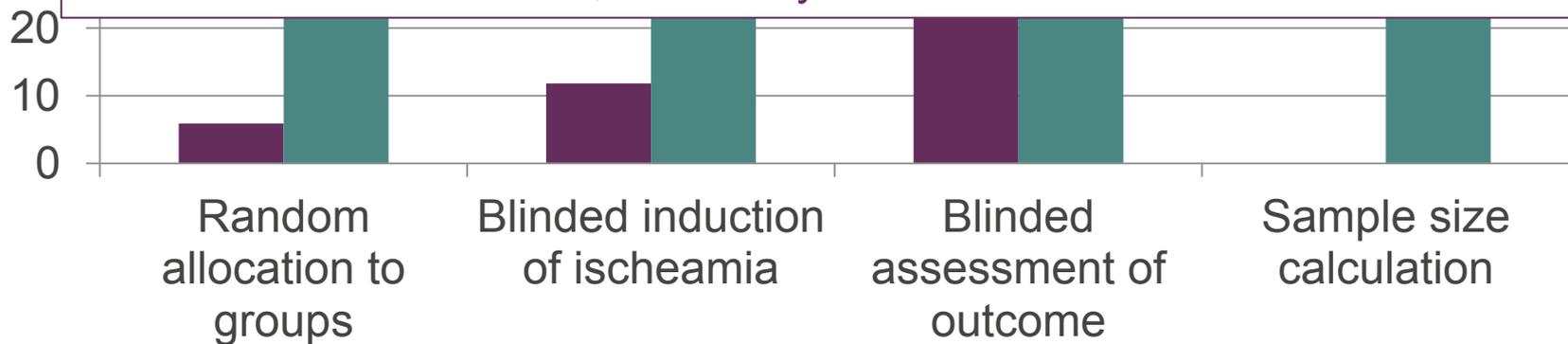
Reporting quality

Studies excluded based on:

- Outcome:

  − Not defined

  − Not consistent between studies

  − Not clinically relevant

- Number of animals not reported

In included studies, sources of heterogeneity couldn't be investigated

Percie du Sert N, Rudd JA, Apfel CC, Andrews PL (2011). Cisplatin-induced emesis: systematic review and meta-analysis of the ferret model and the effects of 5-HT(3) receptor antagonists. *Cancer Chemother Pharmacol* **67**(3)**:** 667-686.
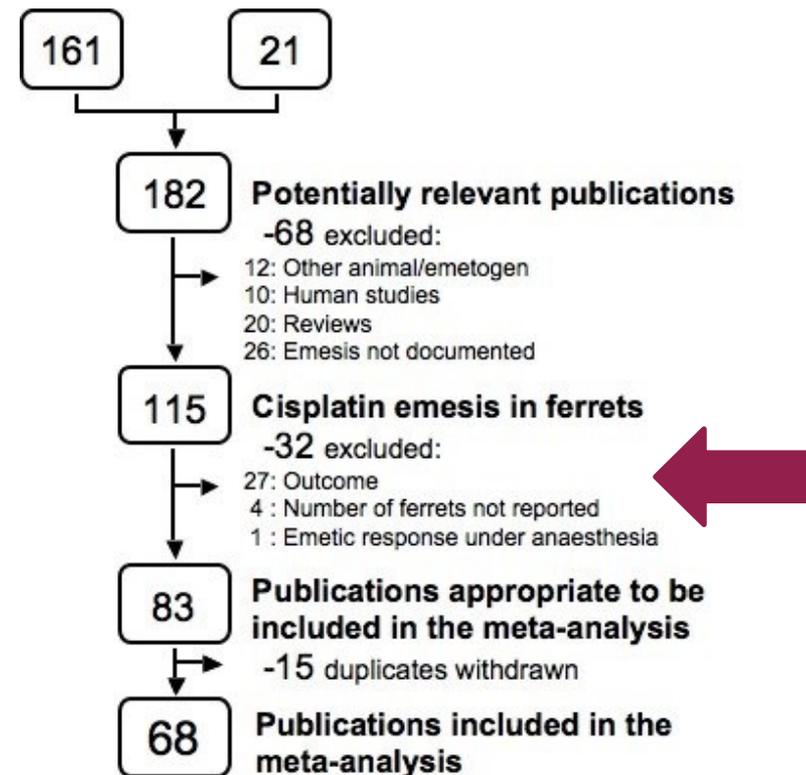
Improving internal validity and reporting

The Experimental Design Assistant

Features include:

- EDA diagram

- Critical feedback on the experimental plan

- Statistical analysis suggestions

- Sample size calculation

- Randomisation sequence generation

- Support for allocation concealment and blinding

- Web-based resources

https://eda.nc3rs.org.uk

Improving internal validity and reporting

The ARRIVE guidelines

The ARRIVE guidelines were developed to improve the reporting of biomedical research using animals.

- Checklist of 20 items, containing key information necessary to describe a study comprehensively and transparently.

- Consensus between:
    - Scientists
    - Statisticians
    - Journal editors
    - Research funders

- Used to ensure transparent and comprehensive reporting

https://www.nc3rs.org.uk/arrive-guidelines

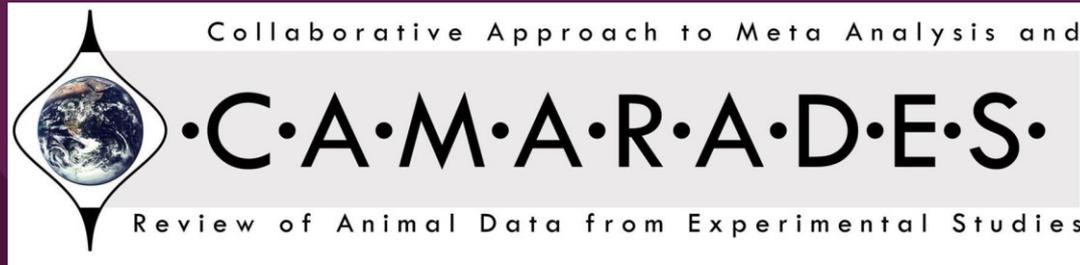# Improving internal validity and reporting
The ARRIVE guidelines

The guidelines include:

- Information which relates to internal validity

- Information which would allow a study to be repeated

- Information about the context and scientific relevance of the study

Using the guidelines ensures that a study contains enough information:

- to be appropriately identified in search strategies

- to assess the risk of bias

- to investigate sources of heterogeneity

Acknowledgements:

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Further information:

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THANK YOU

ANY QUESTIONS?

NC 3Rˢ