



# Broad introduction to systematic reviews, the main steps included, and the CAMARADES-NC3Rs Systematic Review Facility (SyRF)

**Malcolm Macleod**

Collaborative Approach to Meta-Analysis and Review of

Animal Data from Experimental Studies

and

University of Edinburgh



# Disclosures



- Member

- UK Commission for Human Medicines
- EMA Neurology SAG

- UK Animals in Science Committee

- Independent Statistical Standing Committee, CHDI Foundation
- Avilex Pharma Research Steering Group (on behalf of Wellcome Trust)



# Why do systematic reviews?



- To provide unbiased summaries of what is already known
  - To guide future research
  - To guide exploitation of research
  - For regulatory/ licencing purposes
- To identify effects not apparent in individual studies
- To identify areas where research and its reporting might be improved



# What you need ...



- A research question
- A search strategy
- Inclusion and exclusion criteria
- A statistical analysis plan



# Stages



- Develop protocol
- Search
- Screen
- Annotate
- Extract
- Analyse
- Publish



.... TO GUIDE FUTURE RESEARCH



## The Evidence-Based Research Network

A number of studies show that researchers, research funders, regulators, sponsors and publishers of research fail to use earlier research when preparing to start, fund, regulate, sponsor or publish the results of new studies. To embark on research without systematically reviewing the evidence of what is already known, particularly when the research involves people or animals, is unethical, unscientific, and wasteful.



# Systematic Review and Meta-Analysis of the Efficacy of Interleukin-1 Receptor Antagonist in Animal Models of Stroke: an Update



Sarah K. McCann<sup>1</sup> • Fala Cramond<sup>1</sup> • Malcolm R. Macleod<sup>1</sup> • Emily S. Sena<sup>1</sup>

“a systematic review and meta-analysis of the effects of IL-1 RA in animal models of ischaemic stroke .... identified a number of potential shortcomings in the supporting animal literature. Specifically, there was a lack of evidence at times of administration beyond 180 min, of testing in animals with co-morbidities including hypertension or diabetes and of testing in larger animals.”

“The range of evidence supporting the administration of IL-1 RA has increased substantially since our previous systematic review and meta-analysis. Discussion with researchers in the field suggests that this has been due to deliberate efforts to test efficacy in circumstances identified as requiring further evidence. IL-1 RA has now been tested in animals with a range of co-morbidities, at times of administration beyond 180 min, with outcomes assessed up to 28 days after injury and where it is administered via a clinically plausible route.”

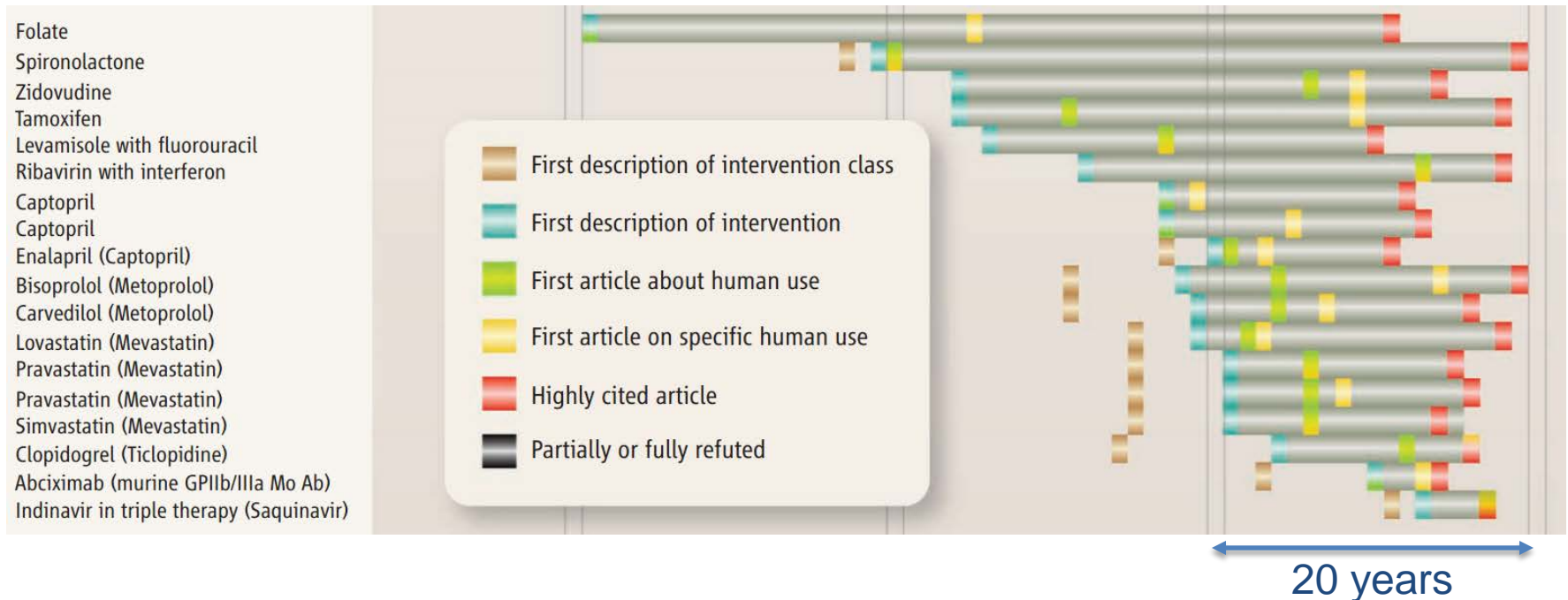




**... TO GUIDE EXPLOITATION OF  
RESEARCH**



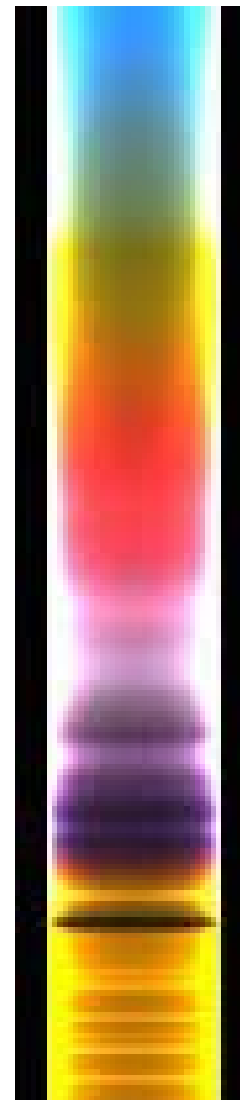
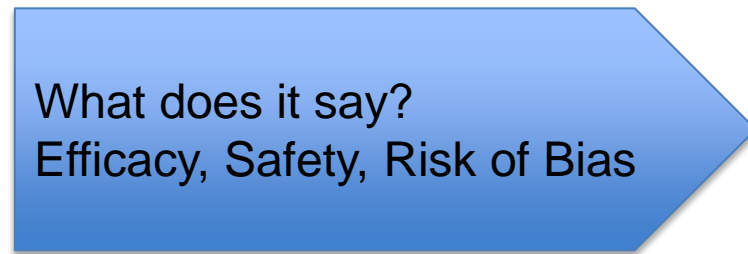
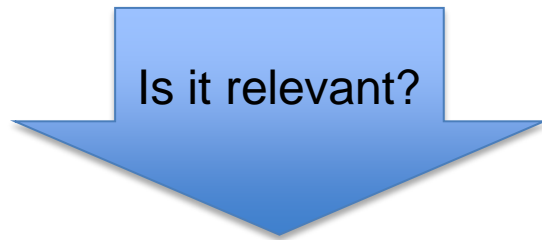
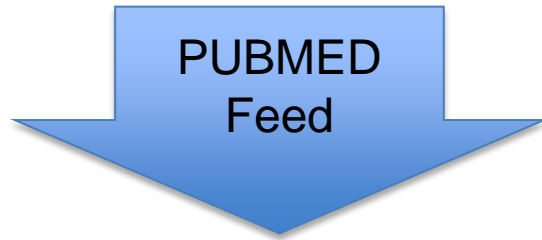
# The pace of translation



Countopoulos-loannidis et al 2008



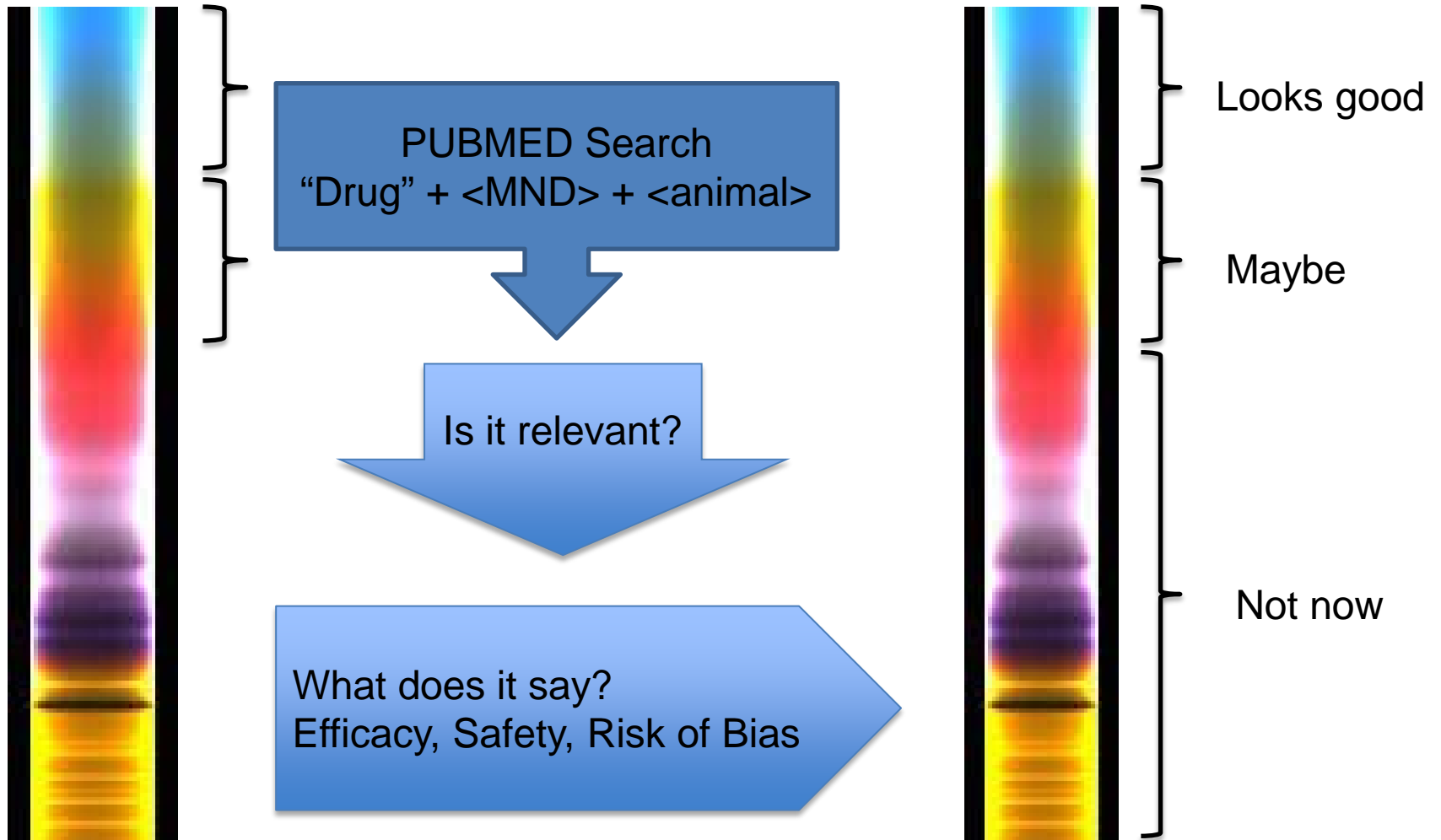
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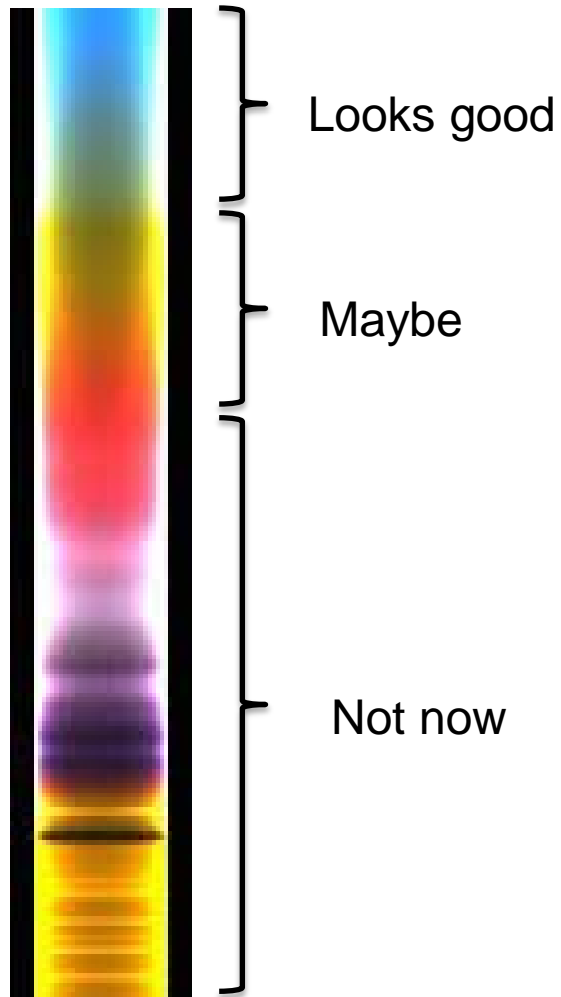


Looks good

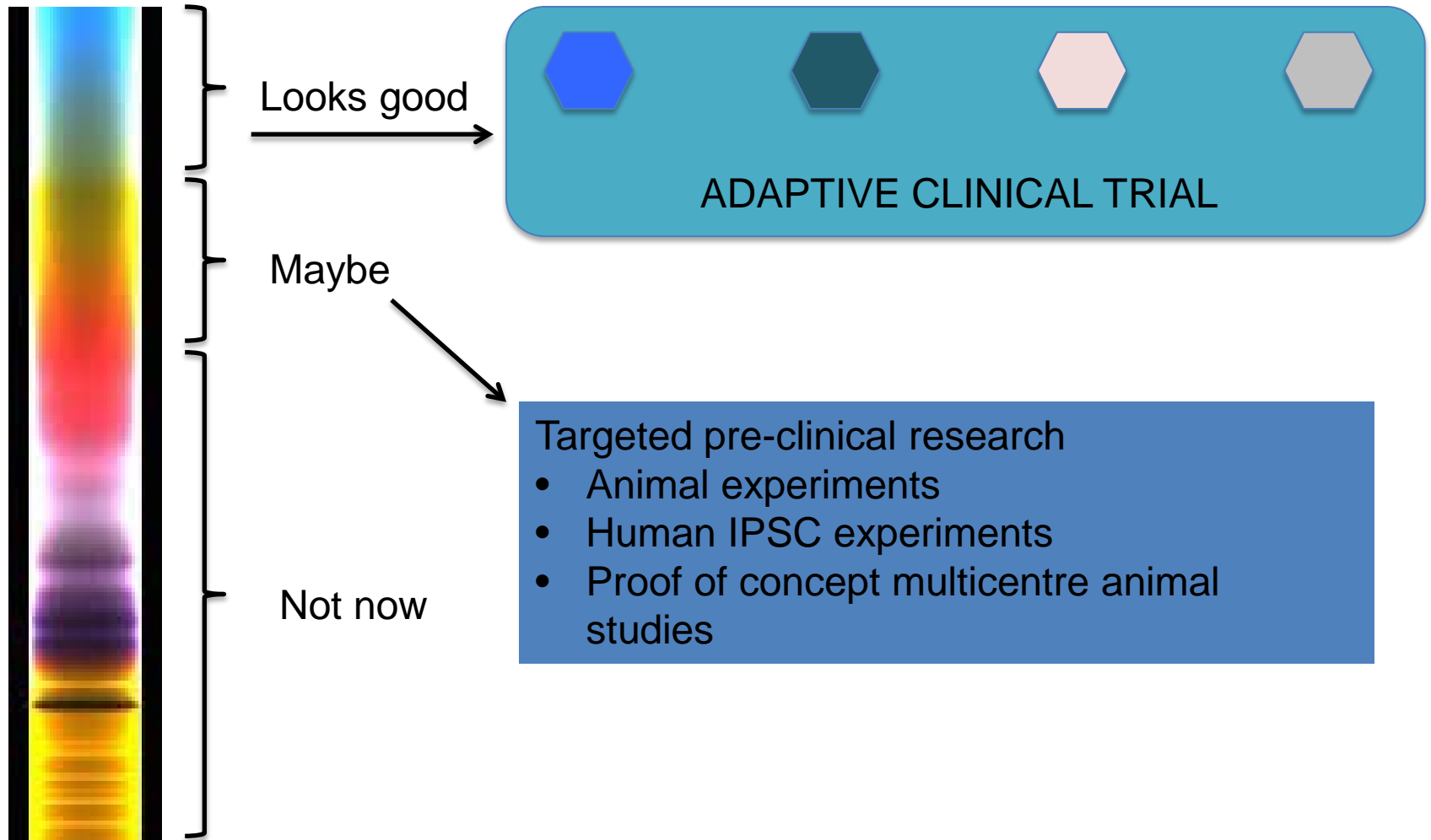
Maybe

Not now





A light blue rounded rectangular box containing four hexagons of different colors (blue, dark blue, pink, grey) and the text "ADAPTIVE CLINICAL TRIAL" centered below them.

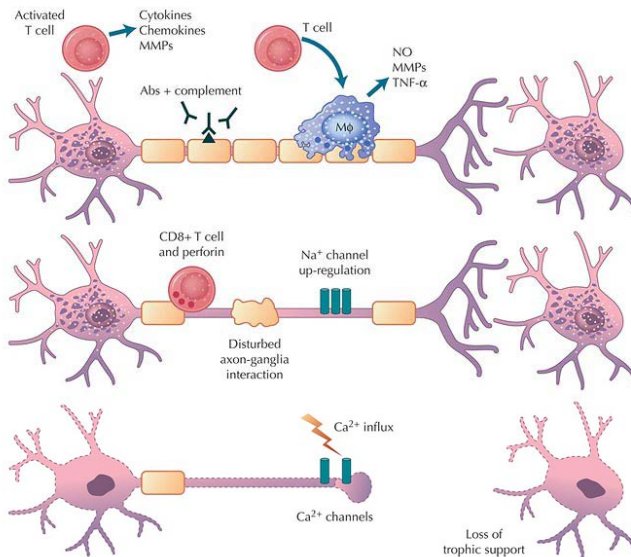
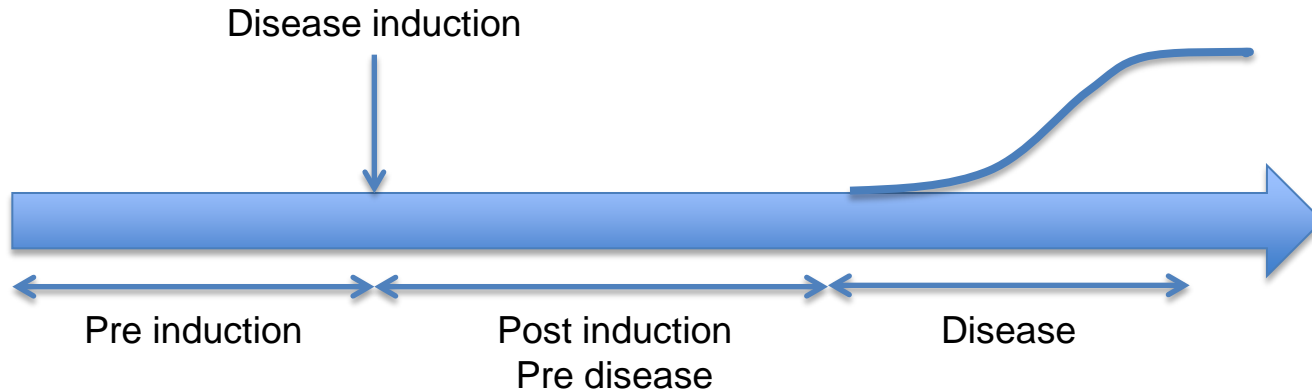




**... TO IDENTIFY EFFECTS NOT  
APPARENT IN INDIVIDUAL STUDIES**



# Shared variance across different outcomes in EAE models

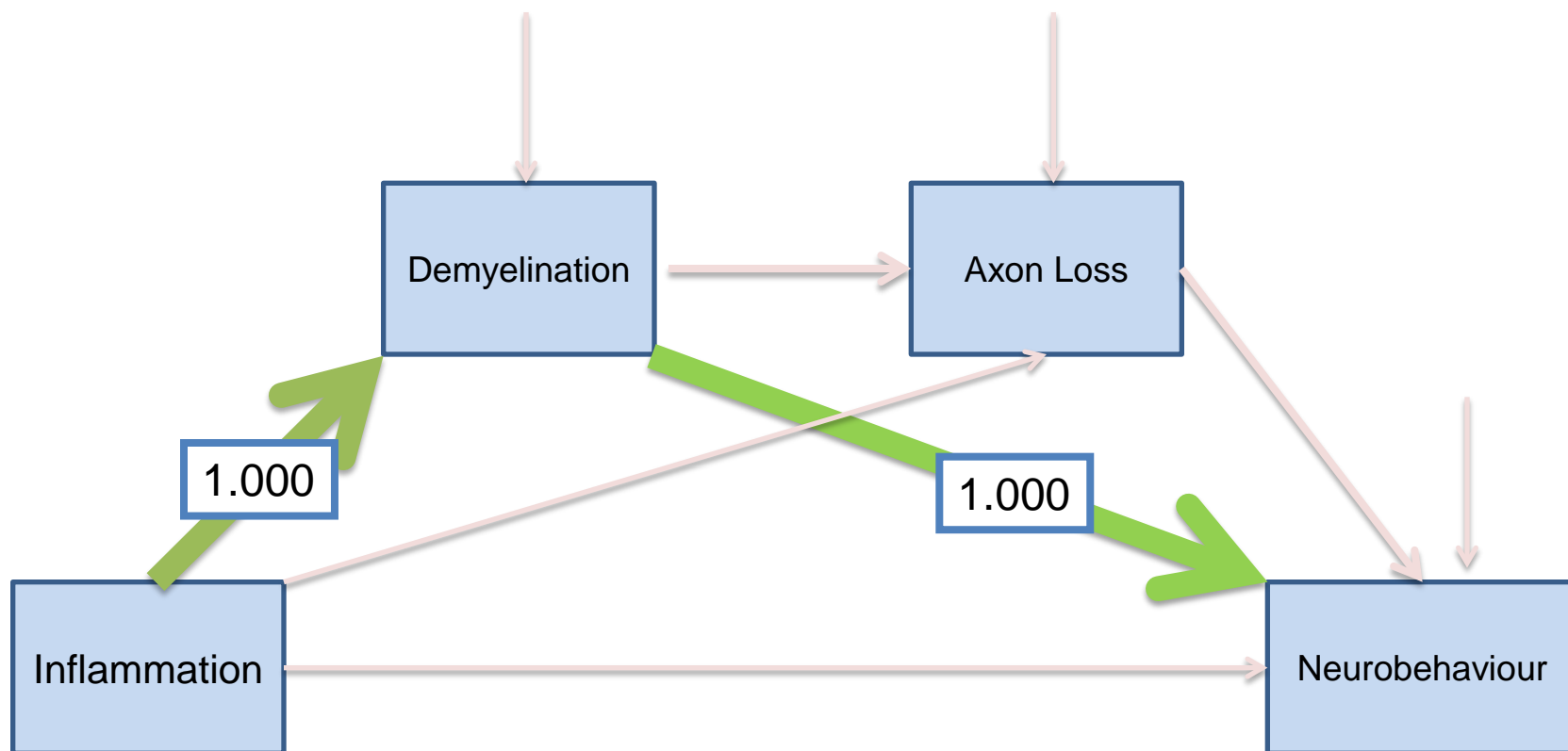


287 mouse experiments  
 Measured effects of treatments on progression of disease and symptoms  
 1.037 (0.863–1.210) SMD improvement in neurobehavioural score





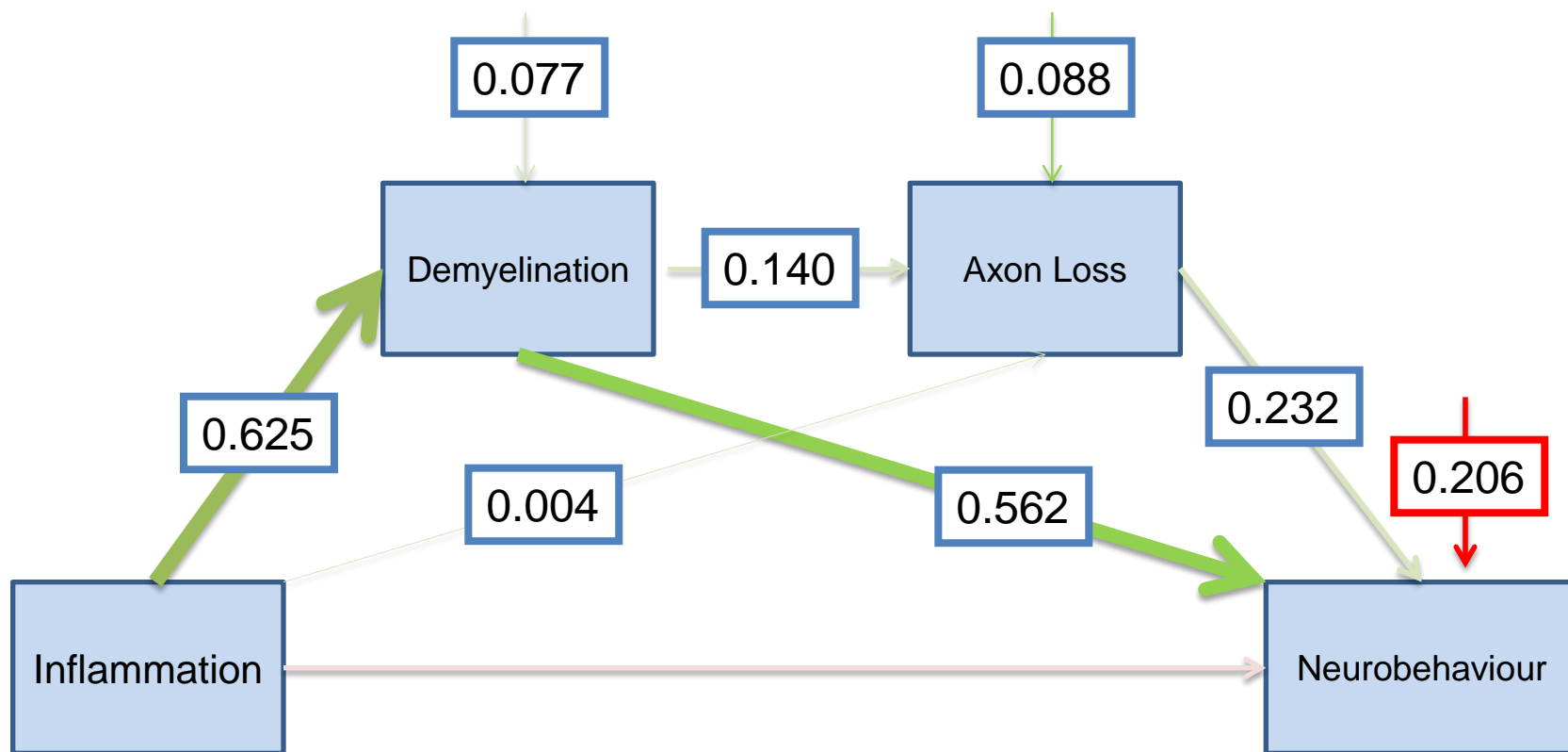
# Pre induction



- Treatments improve neurobehaviour pre disease induction exclusively via effects on demyelination



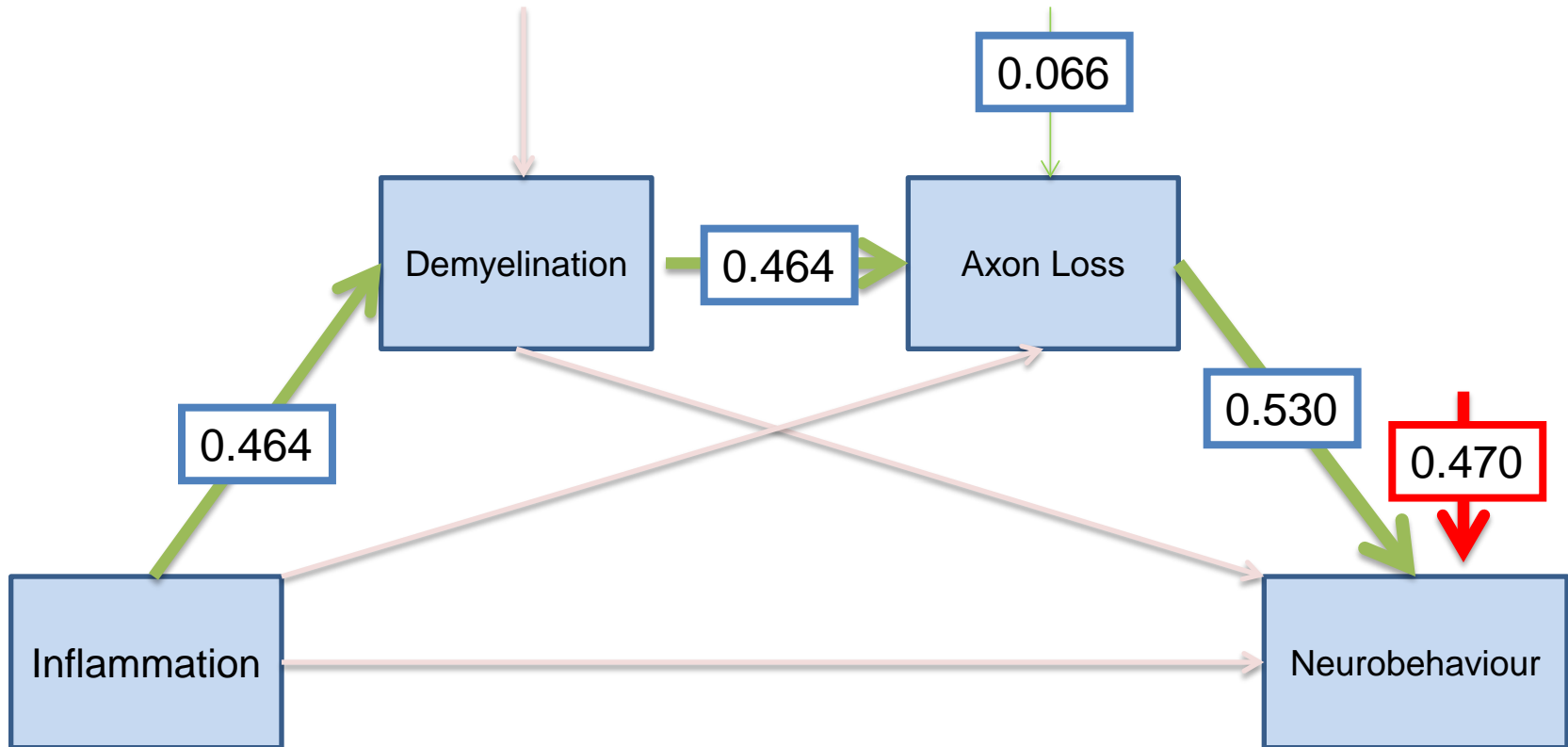
# Post induction Pre disease



- Treatments improve neurobehaviour at post induction stage via effects on demyelination and axon loss



# Disease



- Improvements in neurobehaviour during disease state mediated through axon loss – therefore axon loss should be the drug target for treating the disease.
- Note that **almost half** of drug effects are independent of inflammation, demyelination and axon loss.



**... TO IDENTIFY AREAS WHERE  
RESEARCH AND ITS REPORTING  
MIGHT BE IMPROVED**



# Systematic reviews and the 3Rs



- Reduction: how many animals?
- Replacement: what is the validity of alternative models?
- Refinement: can you get the same information from a less severe procedure?



# Systematic reviews and the ethics of research



“In carrying out the evaluation of a PPL application, to determine whether or not a PPL should therefore be granted, a harm–benefit analysis (HBA) must be undertaken. This is the process of assessing the likely harms that the animals will experience and the likely benefits to be delivered, and then determining whether the likely harms to animals are justified by the benefits likely to accrue.”

 **Avoidable waste in the production and reporting of research evidence**

*Iain Chalmers, Paul Glasziou*

Appropriate design and methods

Accessible full publication

Unbiased and useable reports

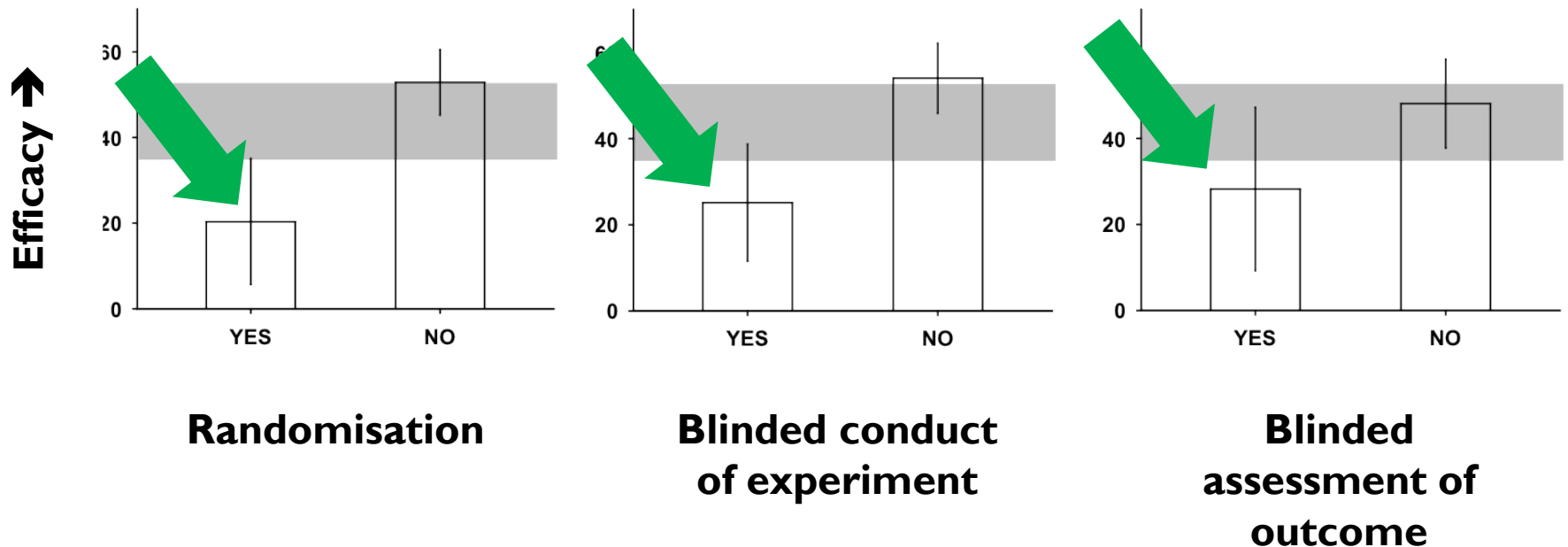
} ~85% research waste



# Risk of bias in animal studies



- Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)



Macleod et al, 2008



# The scale of the problem

## RAE 1173

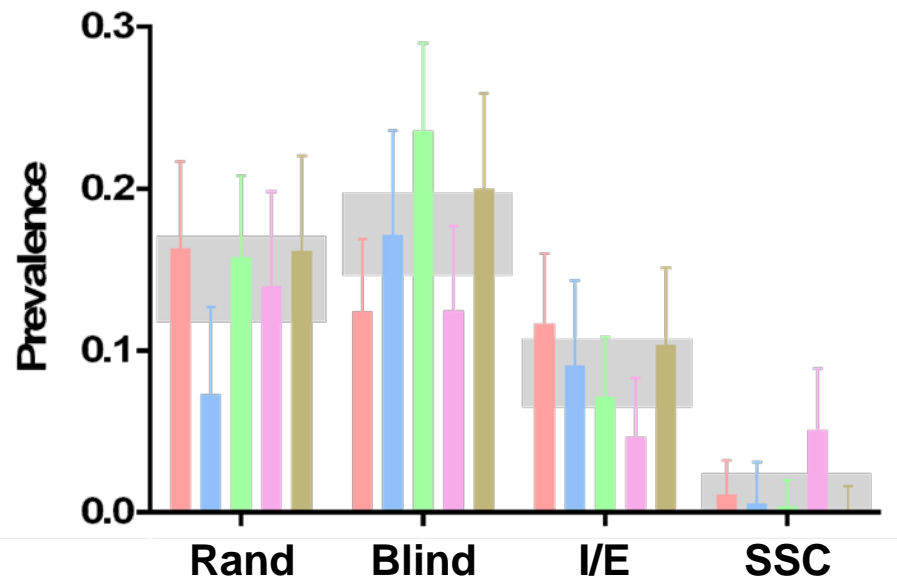


rae2008  
Research Assessment Exercise

“an outstanding contribution to the internationally excellent position of the UK in biomedical science and clinical/translational research.”

“impressed by the strength within the basic neurosciences that were returned ...particular in the areas of behavioural, cellular and molecular neuroscience”

1173 publications using non human animals, published in 2009 or 2010, from 5 leading UK universities



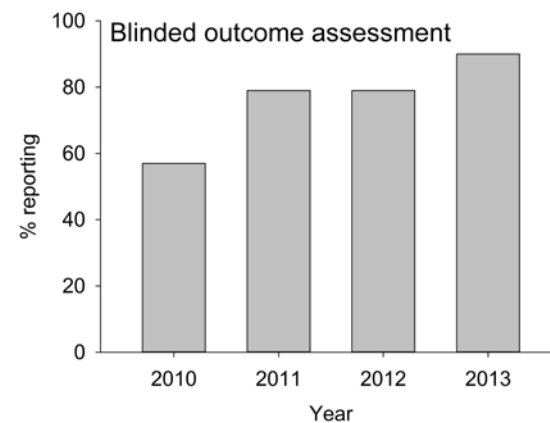
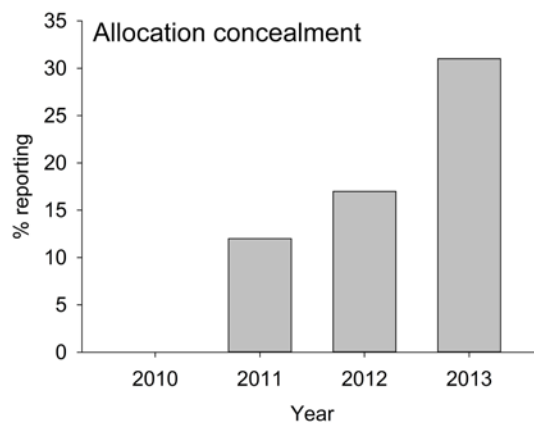
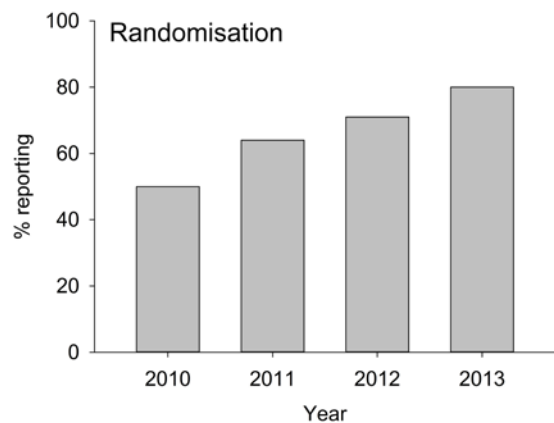




# Comments, Opinions, and Reviews

## Good Laboratory Practice Preventing Introduction of Bias at the Bench

Malcolm R. Macleod; Marc Fisher; Victoria O'Collins; Emily S. Sena; Ulrich Dirnagl;  
Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Traystman; Kazuo Minematsu;  
Geoffrey A. Donnan; David W. Howells

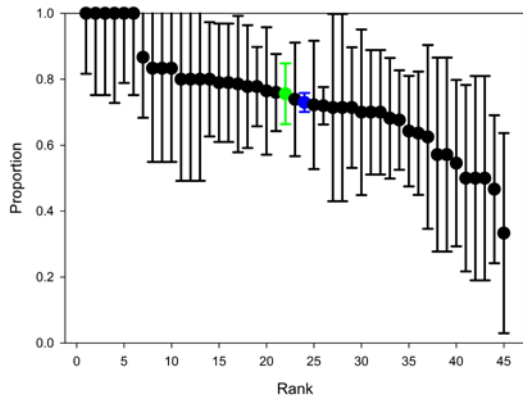


Minnerup et al, 2016

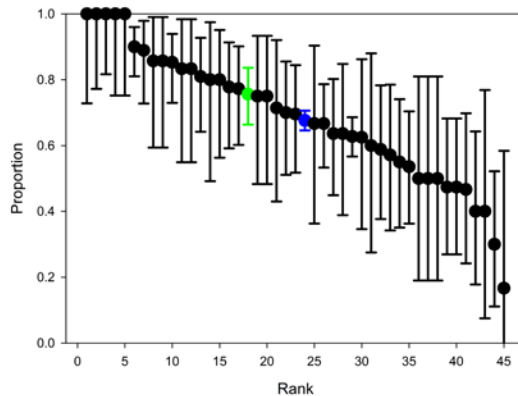


# ... by Journal

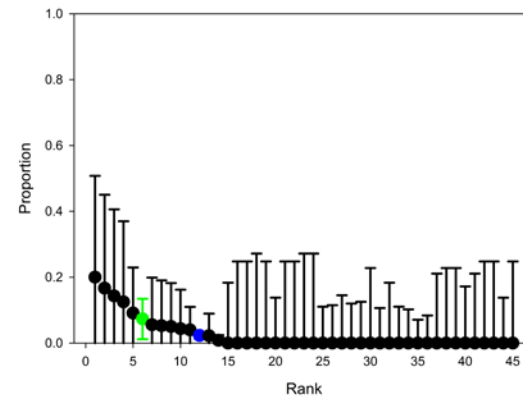
### Randomisation



### Blinding



### Power calculation



Total in Blue  
PLoS One in Green



# The replication difficulty ....

- Psychology replication study
- Cancer replication study
- Amgen
- Bayer
- Etc...
- Watch this space ....

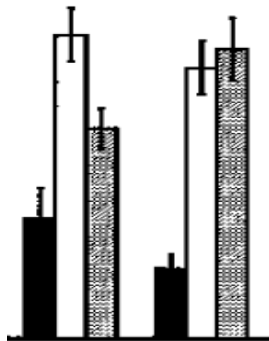


What are the causes?

- ? Fraud
- ? False positive studies +/- dubious research practices
- ? Meta- (sectoral) problems like perverse incentives and publication bias
- ? True biological heterogeneity of observed effects

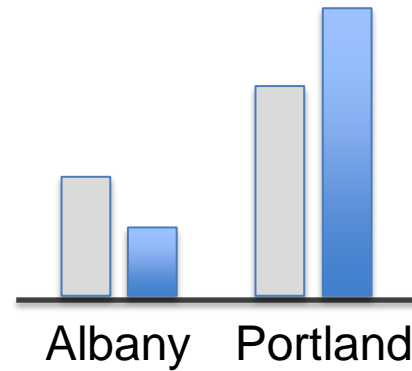


# Crabbe (Science 1999)



129/Sv-ter

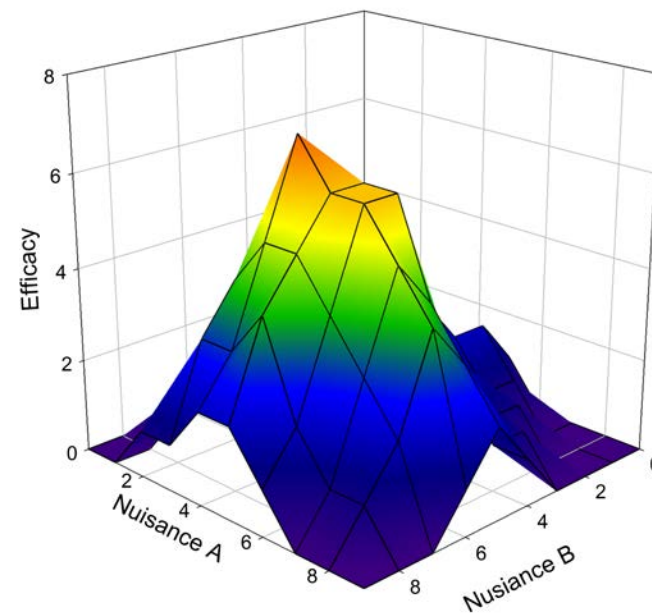
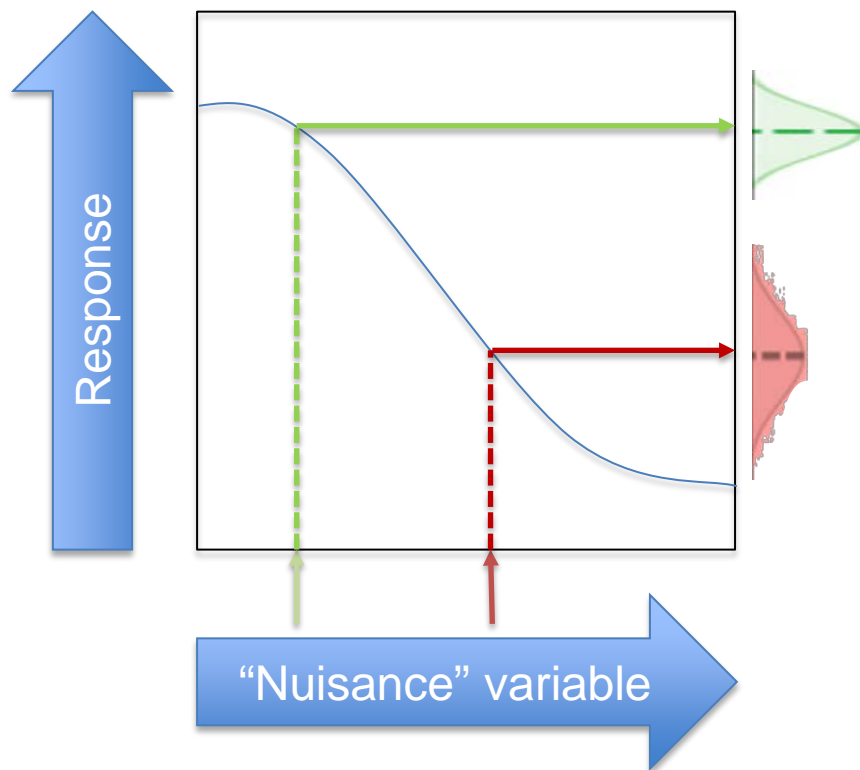
5HT1B-/-

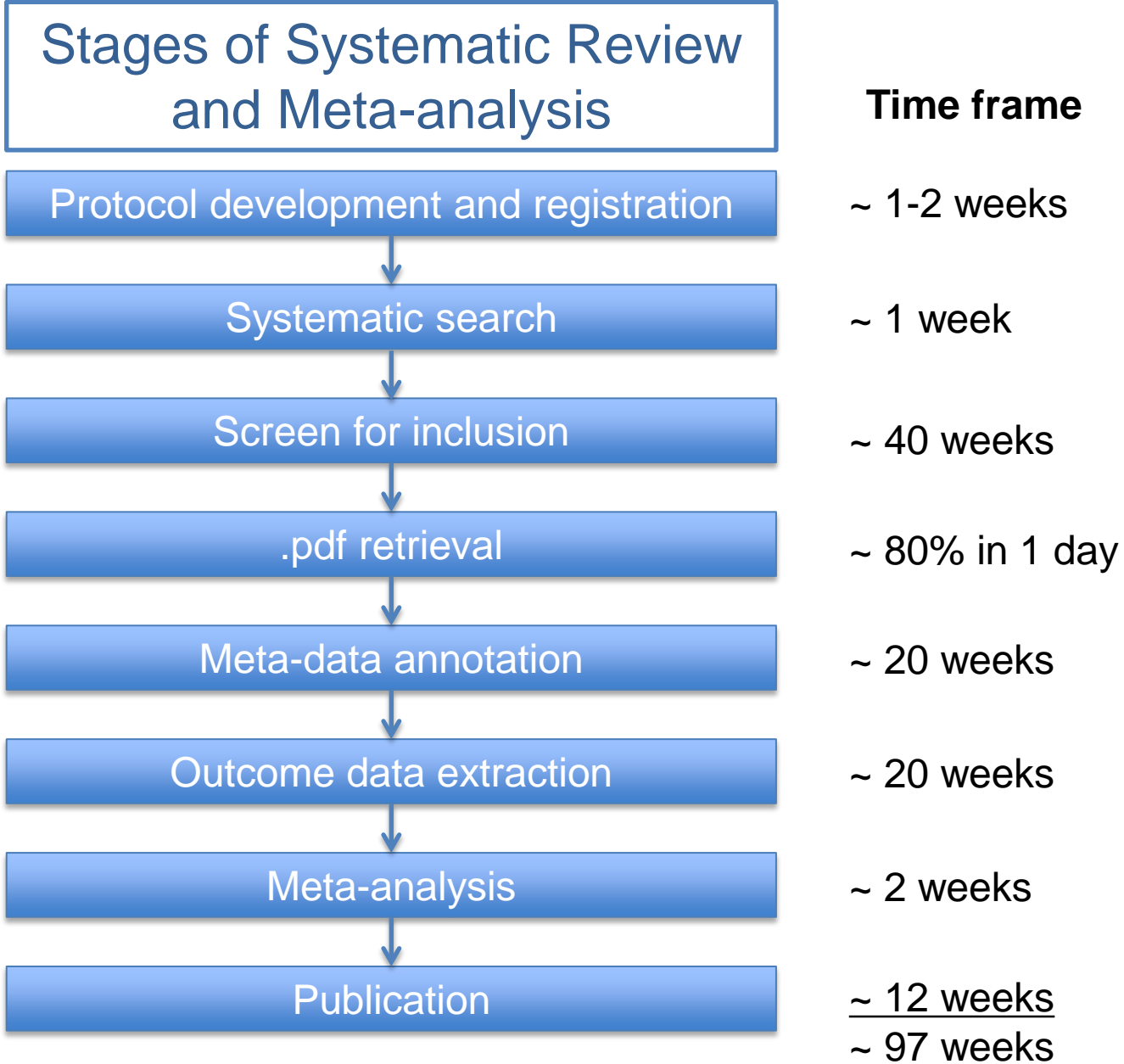


Task	Measure	Eight Genotypes	Three Sites	Two Sexes	Local vs Shipped	Genotype x Site	Genotype x Sex	Genotype x Ship	Multiple R <sup>2</sup>
Open field	Distance in 15 min	.600	.157	---	---	.059	.045	---	.604
Open field	# vertical movements	.788	.281	.039	---	---	---	---	.772
Cocaine	Difference from Day 1	.338	.053	---	---	.086	---	---	.342
Plus maze	Total arm entries	.385	.327	---	---	.210	---	---	.660
Plus maze	Time in open arms	.082	.212	---	---	.066	---	---	.266
Water maze	Mean escape latency	.221	---	---	.026	---	---	---	.177
Alcohol preference	Alcohol consumed (g/kg)	.483	---	.043	---	---	---	---	.451
Body size	Weight (g)	.408	.204	.637	---	.071	.070	---	.698



# Reaction norms (Voelkl 2016)



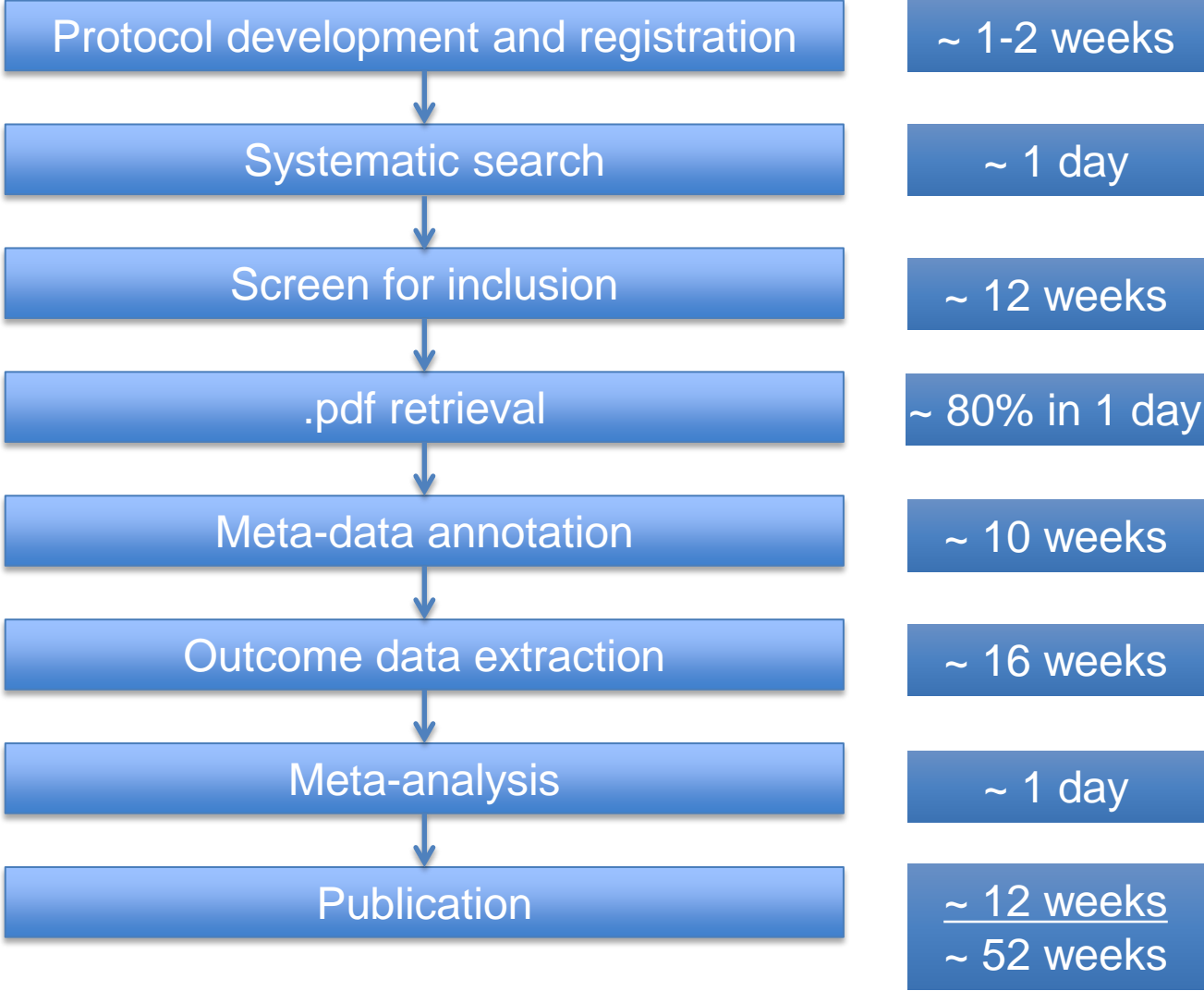




# Stages of Systematic Review and Meta-analysis



SYSTEMATIC  
Review Facility





# Stages of Systematic Review and Meta-analysis

Protocol development and registration

Systematic search

Screen for inclusion

.pdf retrieval

Meta-data annotation

Outcome data extraction

Meta-analysis

Publication

“Living” search

“Living” publication





# PROSPERO registration



## PROSPERO

International prospective register of systematic reviews

**NHS**  
National Institute for  
Health Research

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## Pre-clinical review

Please complete all mandatory fields below (marked with an asterisk \*) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below to see guidance on completing each section.

[Show help](#)

### 1. \* Review title.

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

No title entered yet

### 2. Original language title.

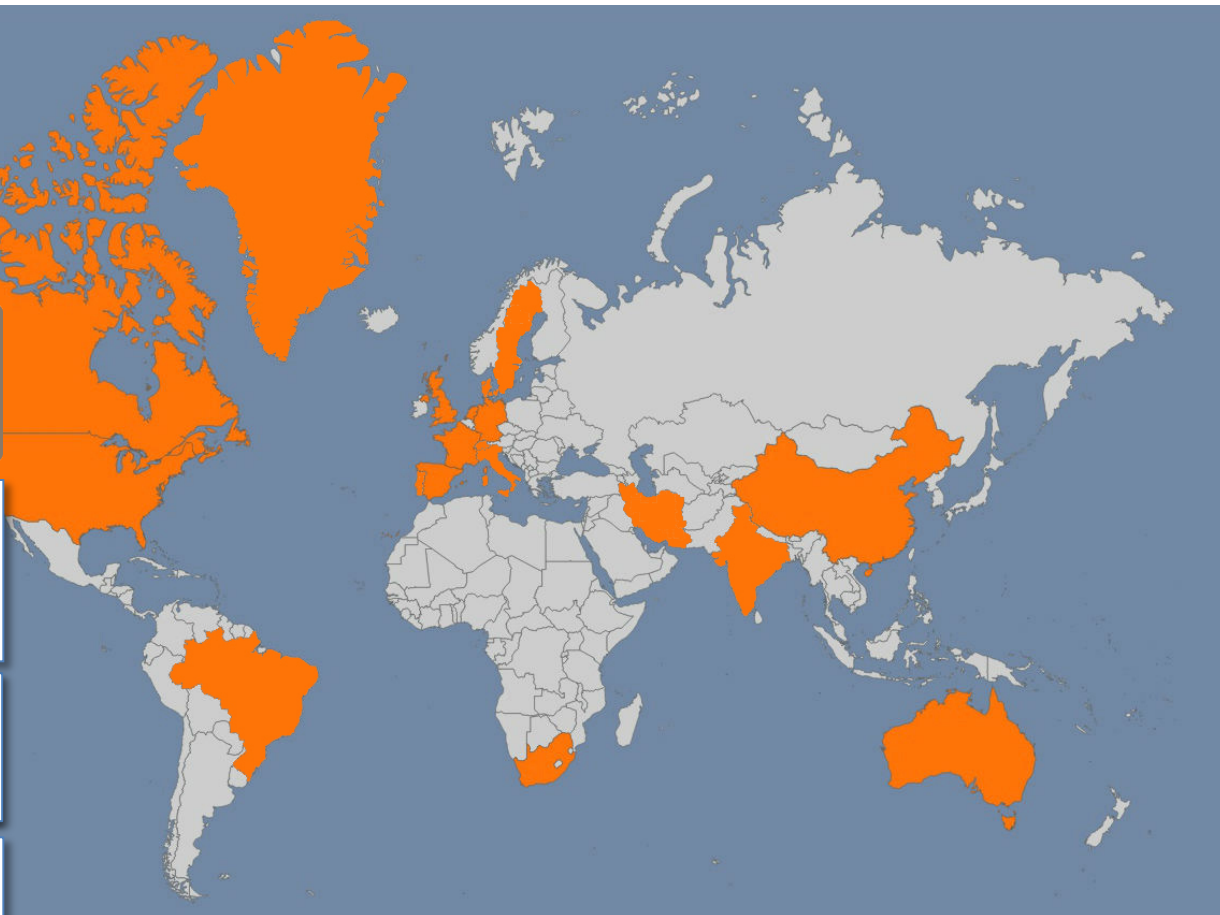
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

### 3. \* Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.



If you are planning a systematic review or meta-analysis of animal data, CAMARADES are here to help: [malcolm.macleod@ed.ac.uk](mailto:malcolm.macleod@ed.ac.uk)



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