CAMARADES: Bringing evidence to translational medicine

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
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.... TO GUIDE FUTURE RESEARCH
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.
“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-Ioannidis et al 2008

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MND SMART

- PUBMED Feed
- Is it relevant?
- What does it say? Efficacy, Safety, Risk of Bias

- Looks good
- Maybe
- Not now
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PUBMED Search
“Drug” + <MND> + <animal>

Is it relevant?

What does it say?
Efficacy, Safety, Risk of Bias

Looks good
Maybe
Not now
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ADAPTIVE CLINICAL TRIAL

- Looks good
- Maybe
- Not now
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ADAPTIVE CLINICAL TRIAL

- Targeted pre-clinical research
  - Animal experiments
  - Human IPSC experiments
  - Proof of concept multicentre animal studies

- Looks good
- Maybe
- Not now
... TO IDENTIFY EFFECTS NOT APPARENT IN INDIVIDUAL STUDIES
Shared variance across different outcomes in EAE models

Disease induction

Pre induction  Post induction  Pre disease  Disease

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

Randomisation

Blinded conduct of experiment

Blinded assessment of outcome

Macleod et al, 2008

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The scale of the problem

RAE 1173

“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

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Good Laboratory Practice
Preventing Introduction of Bias at the Bench

Malcolm R. Macleod; Marc Fisher; Victoria O’Collins; Emily S. Sena; Ulrich Dirmagl; Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Trystman; 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
Reaction norms (Voelkl 2016)
<table>
<thead>
<tr>
<th>Stages of Systematic Review and Meta-analysis</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol development and registration</td>
<td>~ 1-2 weeks</td>
</tr>
<tr>
<td>Systematic search</td>
<td>~ 1 week</td>
</tr>
<tr>
<td>Screen for inclusion</td>
<td>~ 40 weeks</td>
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<tr>
<td>.pdf retrieval</td>
<td>~ 80% in 1 day</td>
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<tr>
<td>Meta-data annotation</td>
<td>~ 20 weeks</td>
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<tr>
<td>Outcome data extraction</td>
<td>~ 20 weeks</td>
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<tr>
<td>Meta-analysis</td>
<td>~ 2 weeks</td>
</tr>
<tr>
<td>Publication</td>
<td>~ 12 weeks</td>
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Stages of Systematic Review and Meta-analysis

1. Protocol development and registration: ~ 1-2 weeks
2. Systematic search: ~ 1 day
3. Screen for inclusion: ~ 12 weeks
4. PDF retrieval: ~ 80% in 1 day
5. Meta-data annotation: ~ 10 weeks
6. Outcome data extraction: ~ 16 weeks
7. Meta-analysis: ~ 1 day
8. Publication: ~ 12 weeks ~ 52 weeks

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Stages of Systematic Review and Meta-analysis

1. Protocol development and registration
2. Systematic search
3. Screen for inclusion
4. .pdf retrieval
5. Meta-data annotation
6. Outcome data extraction
7. Meta-analysis
8. Publication

“Living” search
“Living” publication
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 website 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

   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