CAMARADES Berlin
Facility for systematic review and meta-analysis of animal studies

QUEST Seminar on Responsible Research
February 14th 2023

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Overview

• The CAMARADES network
• Preclinical systematic review and meta-analysis
  • What & why
  • Examples & applications
• CAMRADES Berlin
  • Services and tools
• Working with CAMRADES
  • A systematic review with Mara Meyer Günderoth
The CAMARADES network
CAMARADES
Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Stroke

- First collaboration dedicated to systematic review of preclinical studies
- Founded ~2004
- A systematic approach to identify stroke therapies for clinical trial based on preclinical evidence
- Focus shifted to highlight the limitations of primary stroke research as an impetus to drive improvements in quality
- Name change: *Stroke* to *Studies*
- Growing network of international collaborators
CAMARADES
National coordinating centres

- University of Edinburgh, UK
- University of Tasmania, Australia
- Radboud University Nijmegen Medical Centre
- UCSF, US
- Ottawa Hospital Research Institute, Canada
- BIH QUEST Center, Germany
- Universidade Federal de Santa Catarina, Brazil
CAMARADES
Aims

Bringing evidence to translational medicine

“We aim to improve the reproducibility and quality of preclinical research, by using meta-research methods to inform and improve the standards and processes used by publishers, funders, pharmaceutical companies, and preclinical researchers.”
CAMARADES

Strategies:

Conduct meta-research including systematic reviews to investigate experimental validity across different fields

Develop guidance and provide methodological support for systematic review and meta-analysis of preclinical data

Develop a systematic review platform, specifically designed for preclinical systematic reviews

Develop new automation tools to assist systematic reviews

Promote sharing of data and data analysis tools

Our missions:

- Improve the validity of preclinical research
- Increase the value of preclinical research
- Improve translation from preclinical research to the clinic
Preclinical systematic review

What & why?
Systematic review:
A robust method to objectively and transparently synthesise research evidence to inform decision-making

Meta-analysis:
A statistical method to quantitatively summarise results from individual studies
The biomedical research evidence pipeline

Preclinical research  Clinical research  Clinical practice

Preclinical systematic review  Clinical systematic review
Systematic review

Key characteristics:

a) a clearly stated research question, set of objectives and explicit, reproducible methodology
b) a systematic search to identify all relevant studies
c) assessment of the validity of the findings e.g., risk of bias
d) systematic synthesis of the characteristics and findings of included studies
Systematic review

**Benefits:**

a) Less biased summary and interpretation of current knowledge base
b) Reproducible
c) Better-informed decisions
d) Fully justified new research
Preclinical systematic review

Examples & applications
**Animal studies**
- 11 publications, 29 experiments, 408 animals
- Improved outcome by 44% (95% CI 35-53%)

**Human studies**
- 3 clinical trials involving 5,500 patients
- Final trial neutral
- In the 48 hours following publication
  - AZ share price fell by 17%, market value by $9.6bn
**External validity:** choice of strain

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>Early Gestation</th>
<th>Midgestation</th>
<th>Late Gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WR</td>
<td>SDR</td>
<td>WR</td>
</tr>
<tr>
<td>Gq_EC</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Flow-mediated vasodilation</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Vascular compliance</td>
<td>●</td>
<td>=</td>
<td>●</td>
</tr>
<tr>
<td>Gs_SMC</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Vasoconstrictor</td>
<td>Gq_SMc</td>
<td></td>
<td>=</td>
</tr>
<tr>
<td>Myogenic reactivity</td>
<td>●</td>
<td>=</td>
<td>●</td>
</tr>
</tbody>
</table>

Pregnancy-induced vascular function: increase (↑), decrease (↓), no change (=), inconsistent effects (?), and no effects reported (●)

Van Drongelen et al
2012
Choice of testing frequency

Separation-induced anxiety - multiple testing?

Table 5
Subgroup statistics for total number of vocalizations.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># Articles</th>
<th># Experiments</th>
<th># Animals</th>
<th>SMD[CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>15</td>
<td>43</td>
<td>977</td>
<td>-1.99 [-2.33, -1.64]</td>
</tr>
<tr>
<td>Repeated testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: P &lt; 0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>3</td>
<td>9</td>
<td>233</td>
<td>-1.16 [-1.61, -0.70]</td>
</tr>
<tr>
<td>2-3 times</td>
<td>3</td>
<td>5</td>
<td>102</td>
<td>-2.41 [-3.32, -1.50]</td>
</tr>
<tr>
<td>4 or more times</td>
<td>6</td>
<td>24</td>
<td>540</td>
<td>-2.35 [-2.88, -1.81]</td>
</tr>
<tr>
<td>Not reported</td>
<td>3</td>
<td>5</td>
<td>102</td>
<td>-1.63 [-2.34, -0.92]</td>
</tr>
</tbody>
</table>

NA not applicable; NS not significant; # number; SMD standardized mean difference; CI confidence interval; Subgroups consisting of less than three experiments and/or less than three articles were excluded from between subgroup analyses.
Refining humane endpoints

Mortality in mouse models of stroke

- Decision boundaries determined by a machine learning model
- Mortality can be predicted with high accuracy based on physiological parameters

Mei et al. 2019
Selecting outcome measures and sample sizes

Statistical power of outcome measures for chemotherapy-induced peripheral neuropathy

- The number of animals required to achieve 80% power with a significance level of 0.05 varies substantially across the behavioural tests

Currie et al 2019
Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena¹,²,³, H. Bart van der Worp⁴, Philip M. W. Bath⁵, David W. Howells²,³, Malcolm R. Macleod¹,⁶

- 16% of experiments remain unpublished
- Overstatement of efficacy 31%
Challenges / limitations

- Resource-intensive: personnel, time
- As good as the data that go in – “rubbish in, rubbish out”
- Huge increase in the production of unnecessary, misleading and conflicted reviews
CAMARADES Berlin

Services and tools
CAMARADES Berlin

Research
Systematic review and meta-analysis of preclinical studies:
• Effect of age and comorbidities
• Sex differences
• Framework for systematic review of in vitro studies
• Radiation exposure

Support
Framework for researchers involved in systematic review and meta-analysis:
• Education
• Methodological assistance
• Resources
CAMARADES Berlin
Our services – education

• “Introduction to Preclinical Systematic Review and Meta-analysis” workshop
  - 3 half days online workshop with hands-on activities
    (next dates June 5th-7th 2023)

• In-depth workshops
  - “Systematic Review Protocol Development”
  - “Critical Appraisal of Preclinical Literature”

Charité Medical Library:
- “Systematic literature searches and first steps towards a systematic review”
  (next date Feb 17th, 2023, DE)
CAMARADES Berlin
Our services – education

• **eLearning: Introduction to Preclinical Systematic Review**
  - On-demand lectures and exercises
  - Moodle online learning platform:
    [https://courses.bihealth.org/](https://courses.bihealth.org/)

• **Preclinical systematic review wiki website**
  - Tools and resources to help start a systematic review
  - [https://www.camarades.de/](https://www.camarades.de/)
CAMARADES Berlin
Our services – methodological support

• **Systematic review methods consultation hour**
  - Weekly drop-in sessions
  - Mondays 12:00-13:00 MS Teams

• **One-to-one methodological advice**
  - Support for your systematic review
  - Help with software and tools support
CAMARADES Berlin
Our services – tools and resources

https://syrf.org.uk/
Communities for Open Research Synthesis (COReS)

>> Systematic review as part of the translational research ecosystem

- Primary researchers and synthesists as one community
- New preclinical animal research is informed by a systematic review
- Data from animal research is available for synthesis even when unpublished
Communities for Open Research Synthesis (COReS)

Systematic review as part of the translational research ecosystem

- Fast, open, transparent evidence synthesis
- Effectively inform decision-making in animal research prioritisation and translation
Working with CAMARADES
A systematic review with Mara Meyer Günderoth
Elaboration of a preclinical Systematic Review and Meta-Analysis in cooperation with CAMARADES Berlin

Mara Meyer Günderoth
Centrum für Muskuloskeletale Chirurgie, Charité – Universitätsmedizin Berlin
Julius Wolff Institut

QUEST Seminar
Tuesday, 14.02.2023
Background

Calcitonin

Bone-protective hormone

Severe systemic side effects

Joint specific formulations

Preclinical evidence for the efficacy of Calcitonin in Osteoarthritis and Rheumatoid arthritis?
1. Step

First contact with CAMARADES Berlin


Contacting CAMARADES
2. Steps

First Meeting, Protocol & Workshop

1. Meeting
- Project presentation
- Ideas exchange
- Establishing methods

SYRCLE Protocol
Predefining:
- Research question
- Inclusion & Exclusion criteria
- Methods

CAMARADES Workshop
- Lectures
- Practical training
- Discussions
3. Step

- **Systematic literature search**
- **Data extraction**
- **Study selection**
  - 1. Screening
  - 2. Screening
- **Risk of bias assessment**
- **Meta-analysis**
  - Review Manager (RevMan)

**First Draft**

**Protocol registration at Open Science Framework**
4. Step

One-on-One sessions with CAMARADES
- Regular updates
- Feedback
- Points for revision

Revisions

Quality improvements

Final version
Current status

- Abstract acceptance for 24th EFORT Congress, Vienna 2023 with nomination for the Jacques Duparc Award
- Manuscript submission - Osteoarthritis and Cartilage
- Doctoral scholarship – Sonnenfeld Foundation, Berlin
Summary

- High level of study quality thanks to CAMARADES Berlin
- Various services
- Efficient and reliable collaboration
- Visible success: publication,…
- Exchange of knowledge
Thank you for your attention!

Mara Meyer Günderoth
Centrum für Muskuloskeletale Chirurgie, Charité – Universitätsmedizin Berlin
Julius Wolff Institut

QUEST Seminar
Tuesday, 14.02.2023
CAMARADES Berlin
Get involved!

Learn what a systematic review is
Learn how to start a systematic review
Learn how to critically appraise animal studies
Learn what tools and software are available
Access ongoing support
Contribute to a systematic review
Learn how to systematically search for literature
Learn how to
systematically
search for
literature
Thank you!

Contact:

CAMARADES Helpdesk Support CAMARADES.berlin@charite.de
CAMARADES Berlin Wiki https://www.camarades.de/