CAMARADES Berlin

Facility for systematic review and meta-analysis of animal studies

QUEST Seminar on Responsible Research

February 14th 2023

Sarah McCann **sarah.mccann@bih-charite.de**

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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 CAMARADES**
    - A systematic review with Mara Meyer Günderoth

The CAMARADES network

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CAMARADES

Collaborative Approach to Meta-Analysis and Review of Animal Data fom Experimental ~~Stroke~~ Studies

- 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

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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

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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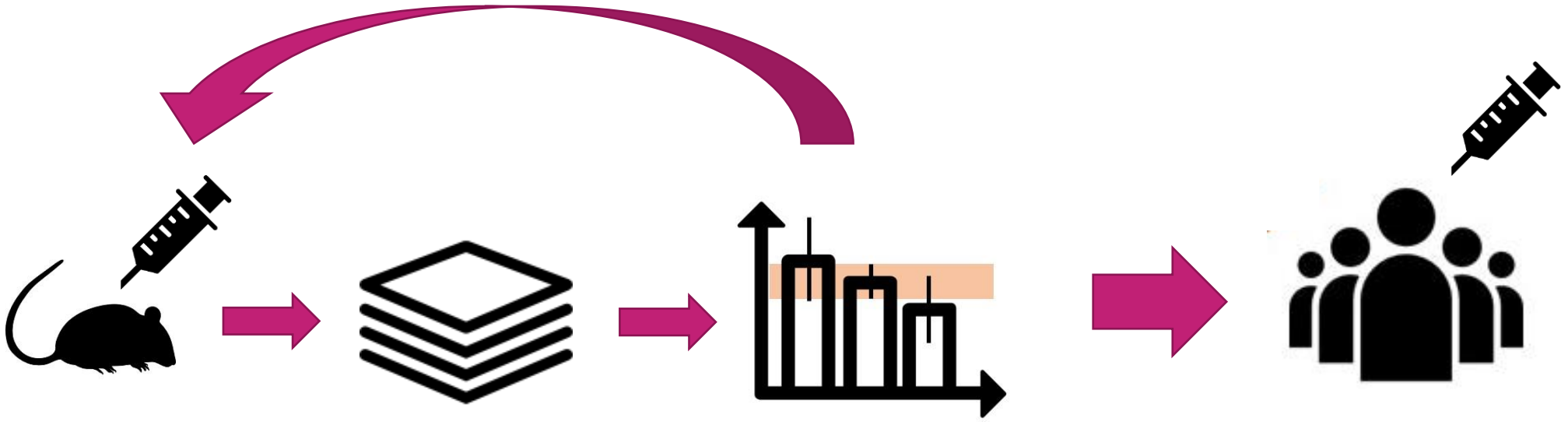
CAMARADES
Aims

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."



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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

Our missions:

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

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

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Preclinical systematic review

What & why?

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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

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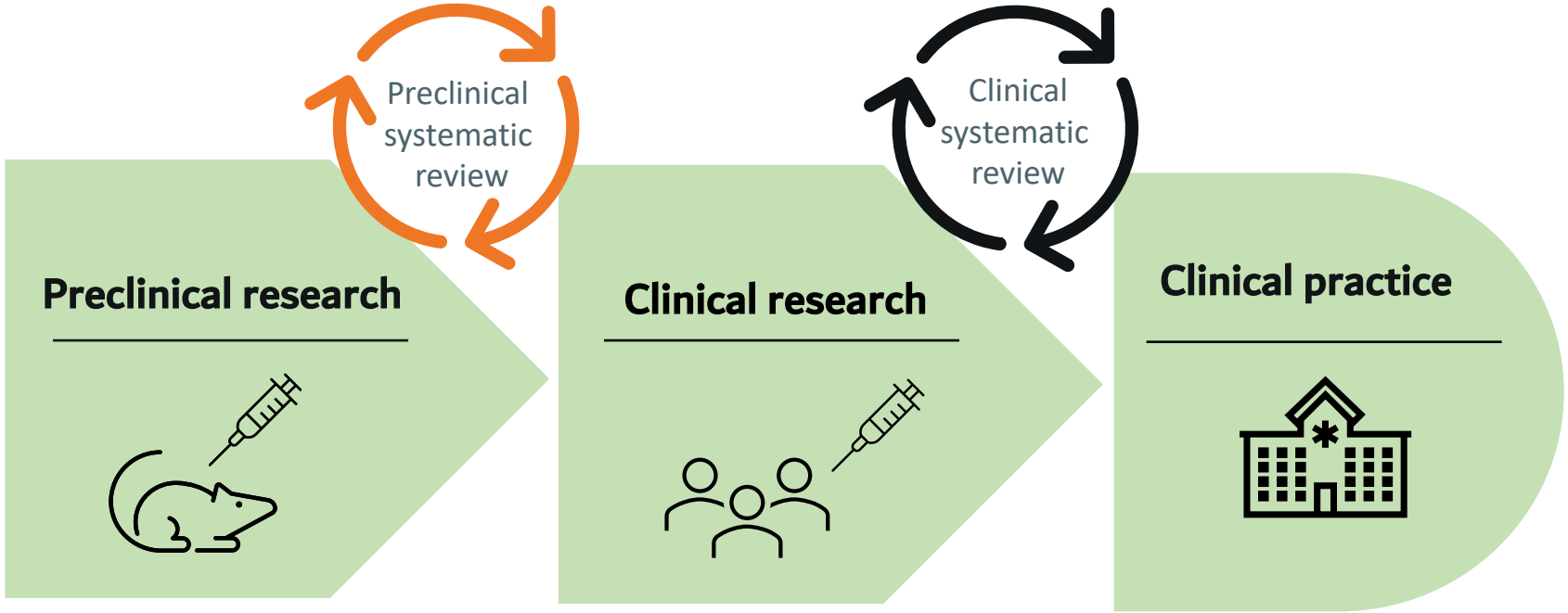
The biomedical research evidence pipeline



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Systematic review

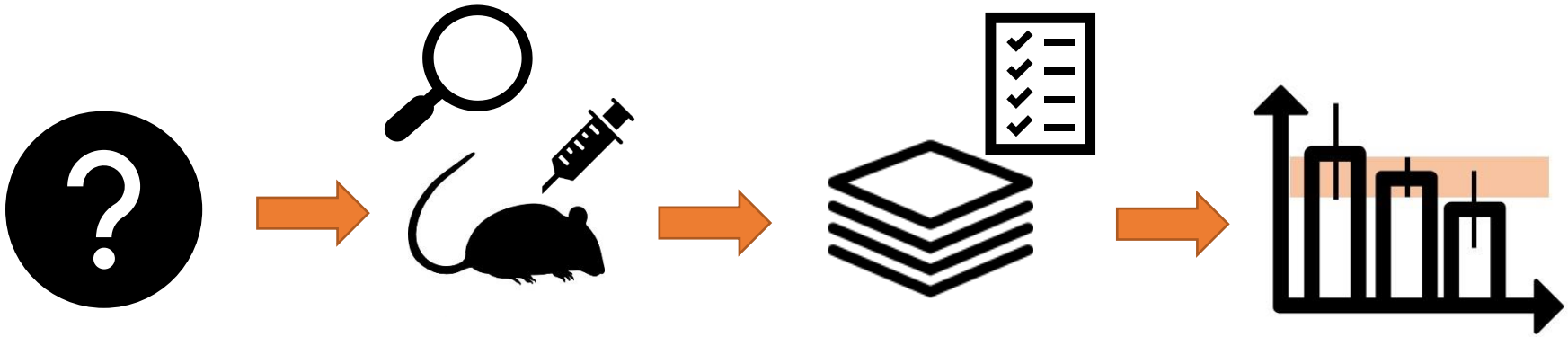
Key characteristics:

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



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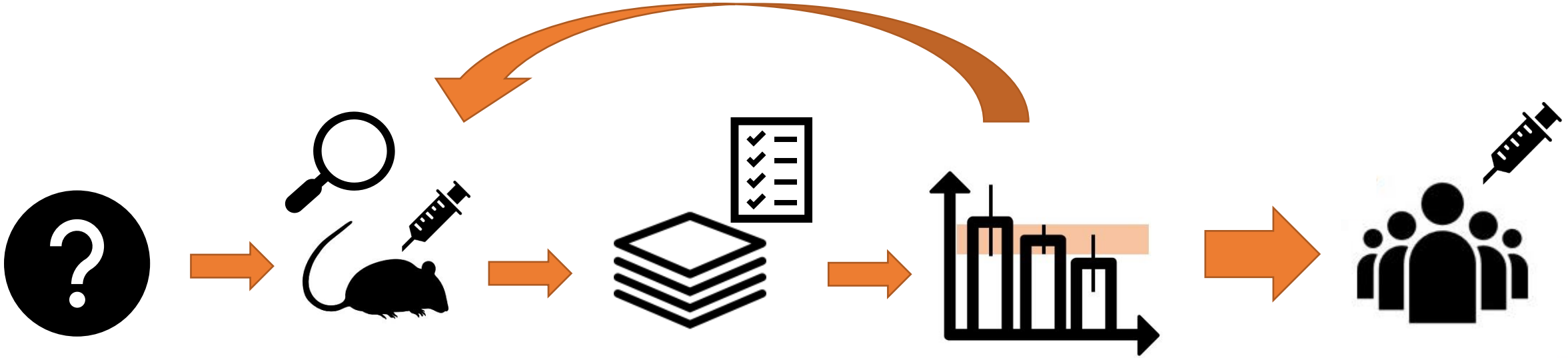
Systematic review

Benefits:

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



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Preclinical systematic review

Examples & applications

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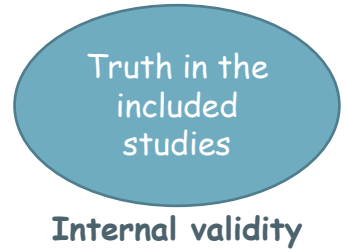
Internal validity: lessons from NXY-059

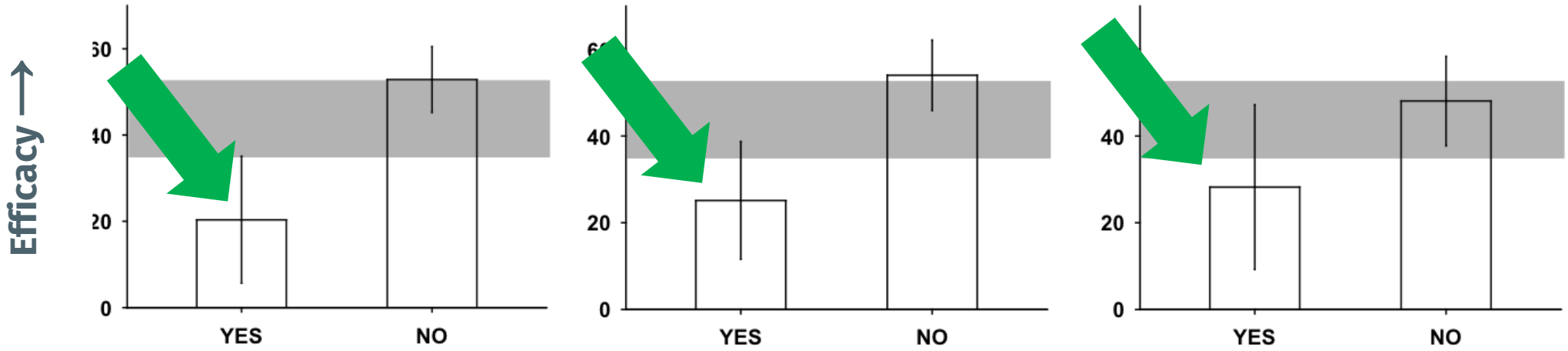


Animal studies

- 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



Randomisation

Blinded conduct of experiment

Blinded assessment of outcome

Macleod *et al* 2008

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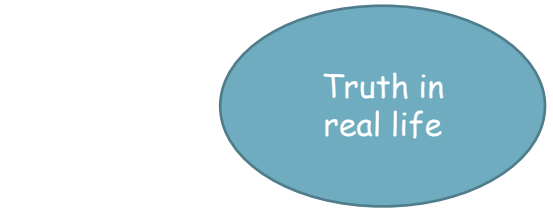
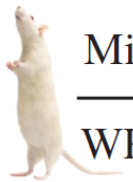
External validity: choice of strain





	Early Gestation		Midgestation		Late Gestation	
	WR	SDR	WR	SDR	WR	SDR
Vasodilator						
Gq_{EC}	•	•	•	=	=	↑
Flow-mediated vasodilation	•	•	↑	•	↑	↑
Vascular compliance	•	↑	=	↑	=	↑
Gs_{SMC}	•	•	↑	•	↓	↑
Vasoconstrictor						
Gq_{SMC}	•	•	=	=	=	↓
Myogenic reactivity	•	=	=	=	=	?

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

Van Drongelen *et al* 2012

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Choice of testing frequency

Animal welfare 3Rs

- Replacement
- Reduction
- Refinement

Separation-induced anxiety - multiple testing?

Table 5
Subgroup statistics for total number of vocalizations.

Subgroup	# Articles	# Experiments	# Animals	SMD[CI]
All studies	**15**	**43**	**977**	**−1.99 [−2.33, −1.64]**
Repeated testing				
Test for subgroup differences $P < 0.00001$				
Once	3	9	233	−1.16 [−1.61, −0.70]
2-3 times	3	5	102	−2.41 [−3.32, −1.50]
4 or more times	6	24	540	−2.35 [−2.88, −1.81]
Not reported	3	5	102	−1.63 [−2.34, −0.92]

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.

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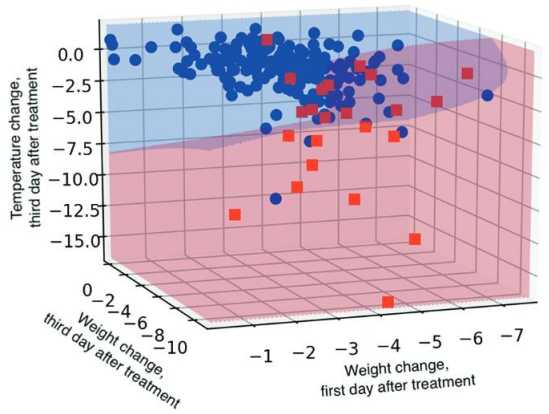
Refining humane endpoints

Animal welfare 3Rs

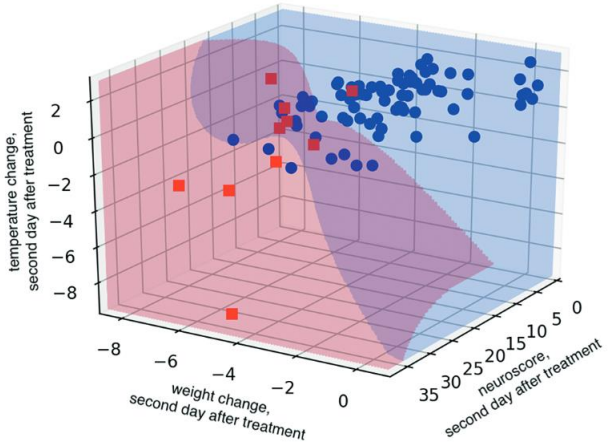
- Replacement
- Reduction
- Refinement

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



Male



Female

Mei *et al* 2019

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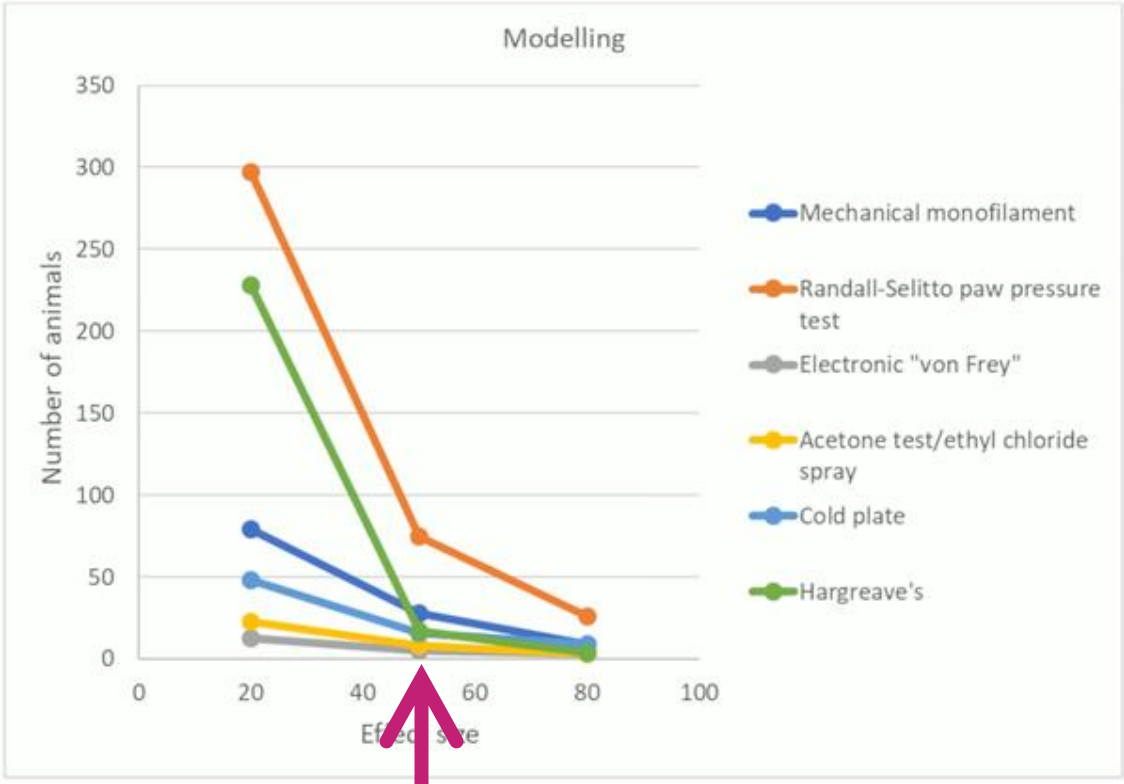
Selecting outcome measures and sample sizes

Animal welfare 3Rs

- Replacement
- Reduction
- Refinement

Statsitical 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

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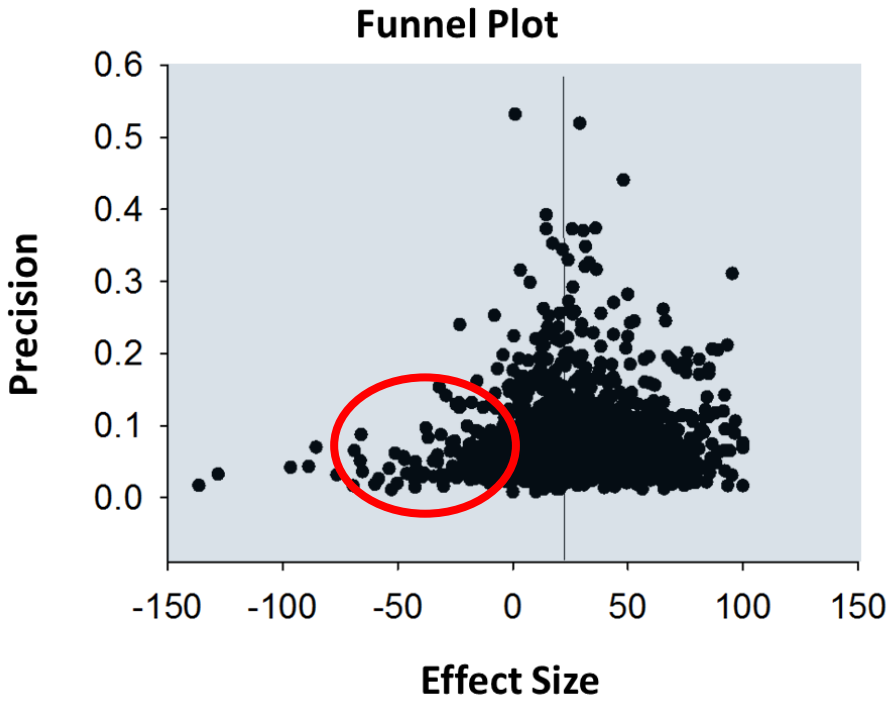
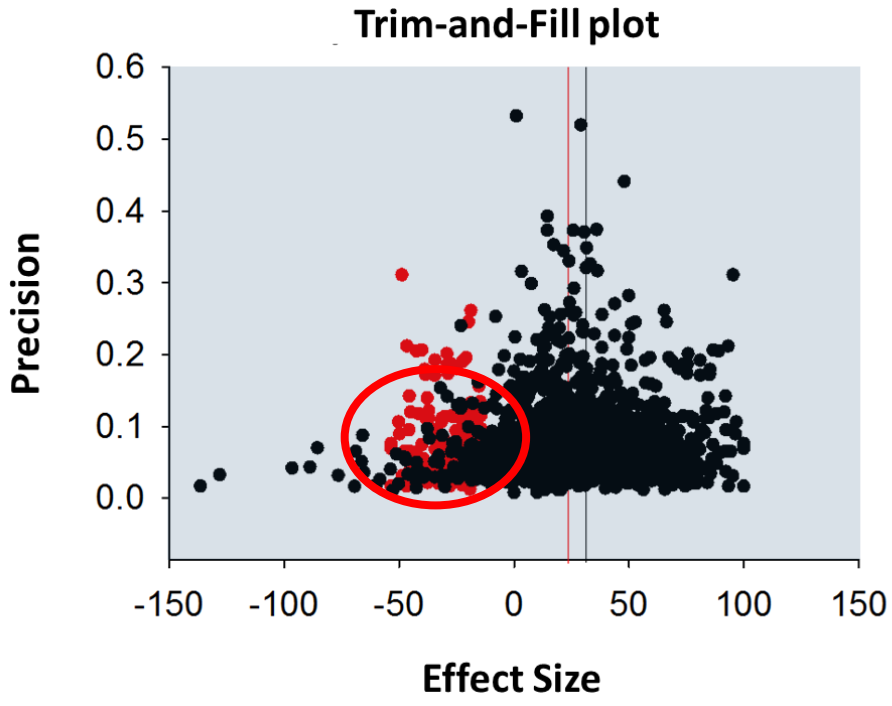
OPEN ACCESS Freely available online

PLoS BIOLOGY

Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena[1,2,3], H. Bart van der Worp[4], Philip M. W. Bath[5], David W. Howells[2,3], Malcolm R. Macleod[1,6]*





- **16%** of experiments remain unpublished
- Overstatement of efficacy **31%**

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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

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Services and tools

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CAMARADES Berlin

Alex Bannach-Brown
Post-Doc

Sofija Vojvodic
PhD candidate

Torsten Rackoll
Post-Doc

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

3R Replace Reduce Refine

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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)

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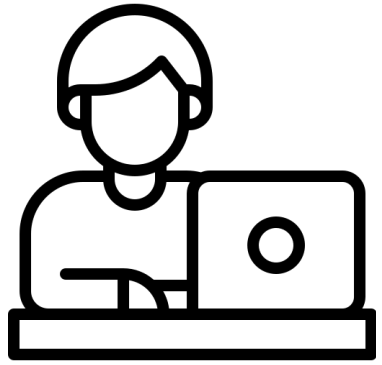
CAMARADES Berlin
Our services – education

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



- **Preclinical systematic review wiki website**
  - Tools and resources to help start a systematic review
  - https://www.camarades.de/

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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

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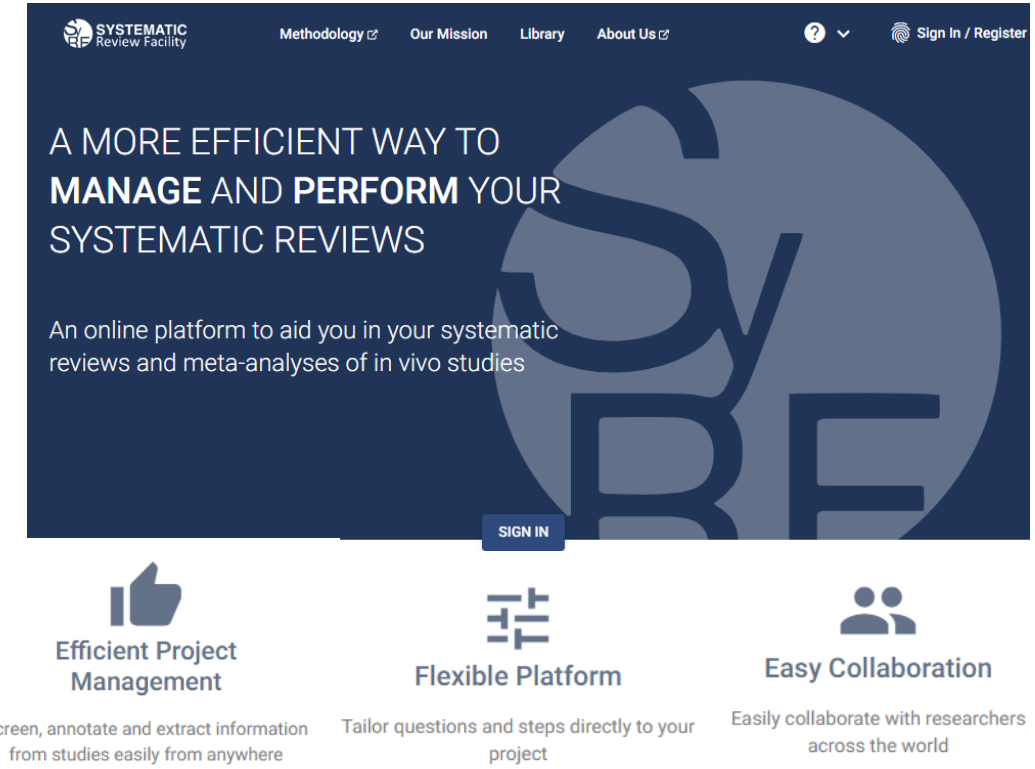
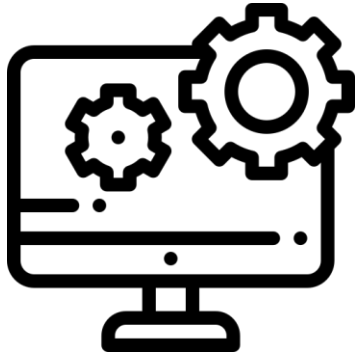
Our services – tools and resources



https://syrf.org.uk/

Local helpdesk



Automated tools

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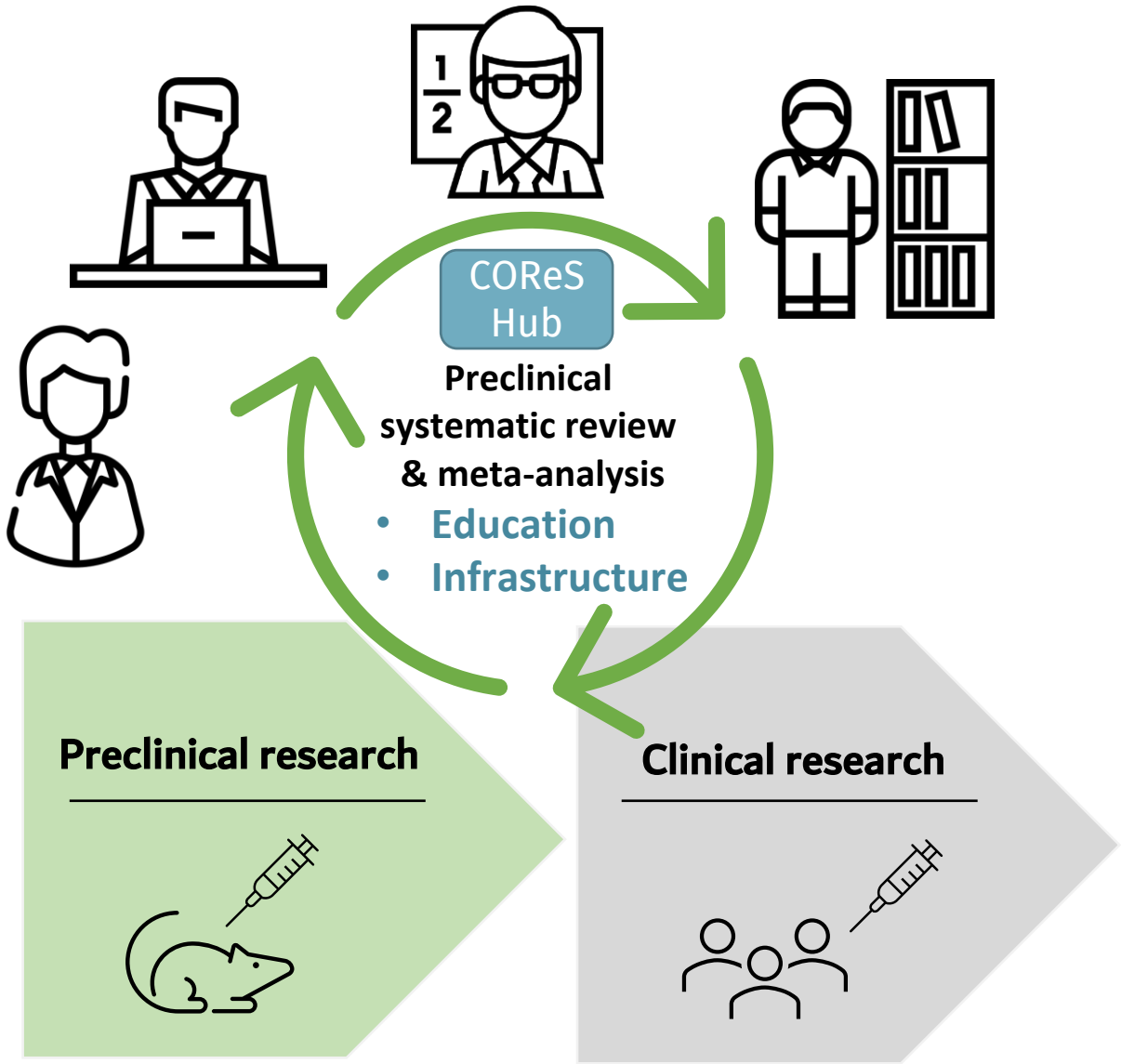
Communities for Open Research Synthesis (CORes)

>> 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

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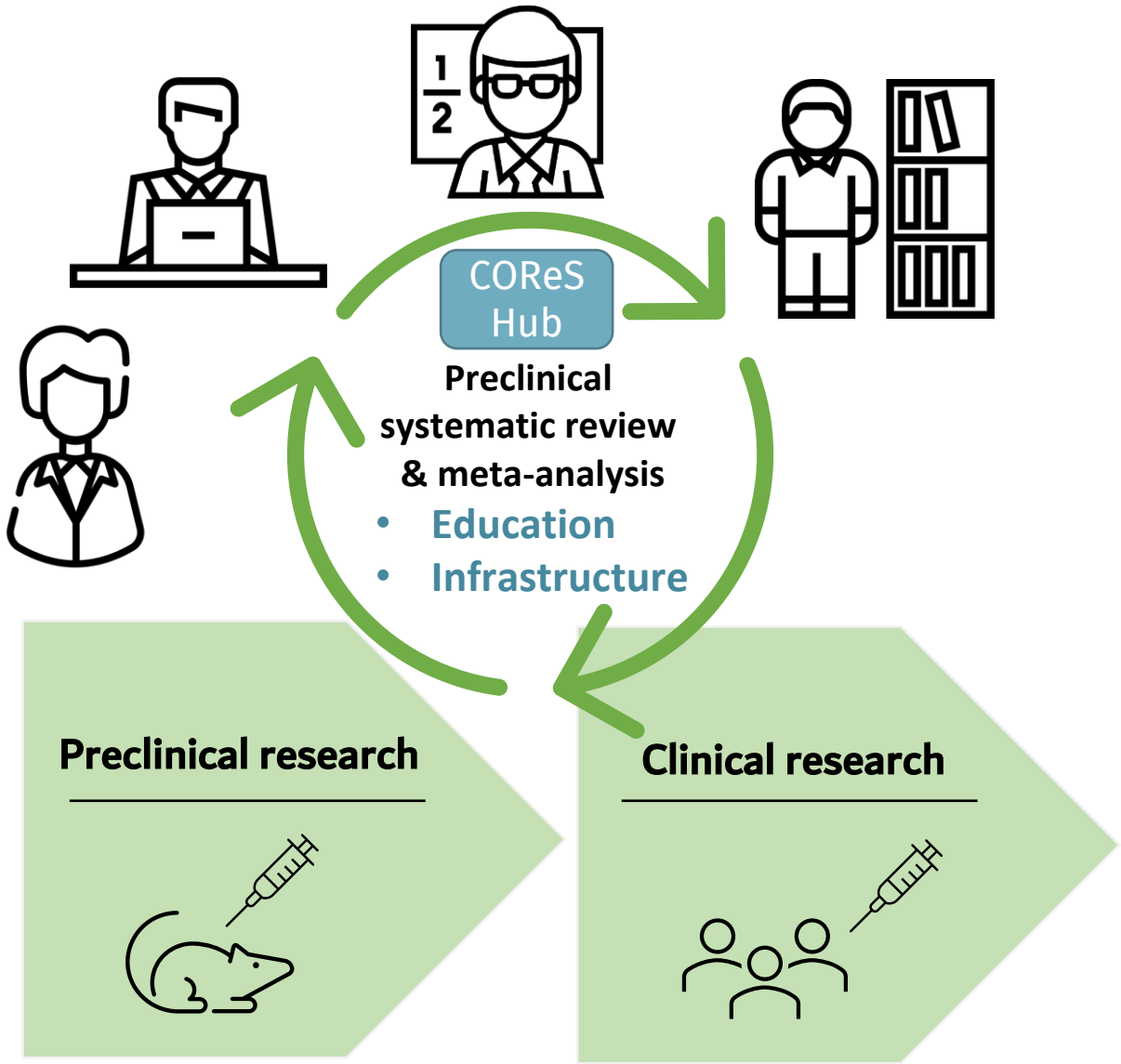
Communities for Open Research Synthesis (CORes)

>> Systematic review as part of the translational research ecosystem



- ✓ Fast, open, transparent evidence synthesis
- ✓ Effectively inform decision-making in animal research prioritisation and translation

VolkswagenStiftung

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Working with CAMARADES

A systematic review with Mara Meyer Günderoth

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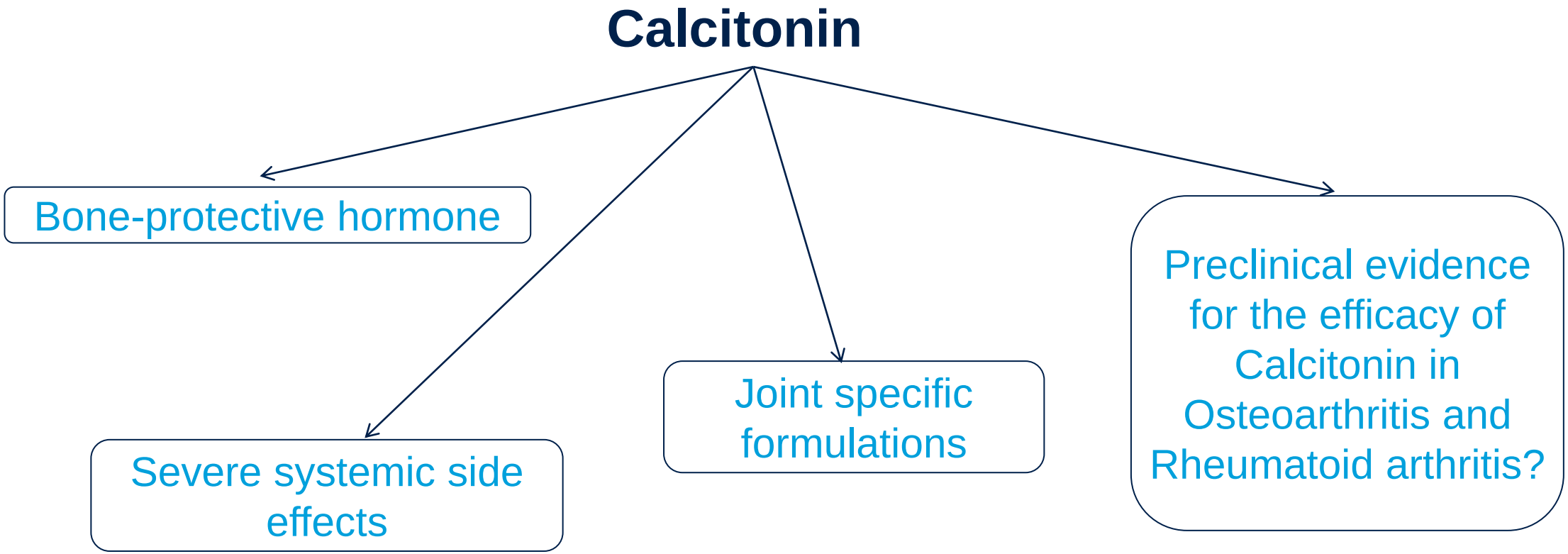
Elaboration of a preclinical Systematic Review and Meta-Analysis in cooperation with CAMARADES Berlin

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

Soliman N, Rice ASC, Vollert J. A practical guide to preclinical systematic review and meta-analysis. Pain 2020; 161: 1949-1954.

Contacting CAMARADES

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CENTRUM FÜR MUSKULOSKELETALE CHIRURGIE

JULIUS WOLFF INSTITUT

2. Steps

SYRCLE Protocol

Predefining:

- Research question
- Inclusion & Exclusion criteria
- Methods

First Meeting, Protocol & Workshop

1. Meeting

- Project presentation
- Ideas exchange
- Establishing methods

CAMARADES Workshop

- Lectures
- Practical training
- Discussions

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3. Step

Systematic literature search

Data extraction

Meta-analysis
- Review Manager (RevMan)

First Draft

Protocol registration at Open Science Framework

Study selection
- 1. Screening
- 2. Screening

Risk of bias assessment

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4 . Step

Revisions

Quality improvements

One-on-One sessions with CAMARADES

- Regular updates
- Feedback
- Points for revision

Final version

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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

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CAMARADES Berlin
Get involved!

Learn what a systematic review is

Learn what tools and software are available

Learn how to critically appraise animal studies

Access ongoing support

Contribute to a systematic review

Learn how to start a systematic review

Learn how to systematically search for literature

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Thank you!

Contact:

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

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