

Meeting Report

Summer School for Systematic Reviews of Animal Studies: Fostering Evidence-Based and Rigorous Animal Research

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Rationale, tasks, and goals

Systematic reviews employ a rigorous and reproducible approach to systematically gather, evaluate, and synthesize all available relevant literature. As such, they represent the highest level of evidence appraisal and are integral in clinical research (Higgins et al., 2019). Systematic reviews are also increasingly employed in animal research (Ritskes-Hoitinga and Pound, 2022a). The application of systematic reviews enhances the robustness of animal research in several ways: First, the pooling of several studies allows identification of trends or effects that may not be detected in individual, smaller studies. Second, systematic reviews are characterized by *a-priori* definition of criteria governing the inclusion of relevant research, thereby mitigating biases. Third, systematic review can yield novel results without the use of additional animals (Ritskes-Hoitinga and Pound, 2022a,b). And finally, systematic reviews provide a way to keep abreast of the skyrocketing number of newly published animal studies that need to be integrated into an evidence-based research framework (Ineichen et al., 2023). With this, systematic reviews enhance the harm-benefit equation for animal studies by increasing the benefit and reducing the harm inherent in animal experiments (Fig. 1) (Eggel and Würbel, 2021).

Despite the benefits of conducting a systematic review, particularly in animal science, their relatively scarce implementation highlights the importance of persistent endeavors to raise awareness and engagement. Therefore, the STRIDE-Lab at the Center for Reproducible Science at the University of Zurich, in collaboration with CAMARADES Switzerland, organized its first sum-

mer school on systematic review of animal studies. The goal of the summer school was to disseminate knowledge on systematic reviews and equip the participants with the skill set necessary to independently conduct systematic reviews and to increase their awareness of its potential in animal science. Twenty animal researchers from Europe with diverse scientific backgrounds (e.g., veterinary medicine, biomedical imaging, behavioral neuroscience, and cancer research) and at various career levels (including master and PhD students, postdoctoral researchers, and professors) attended the course. Participants experienced a balance of lectures and hands-on sessions on methodology of systematic reviews, including both individual and group activities. A panel of invited speakers gave presentations on pertinent topics of animal welfare and systematic review.

Workshop program

On the first day of the summer school, Dr **Benjamin Ineichen** (University of Zurich, Switzerland, head of the STRIDE-Lab and CAMARADES Switzerland) welcomed the participants and highlighted some of the benefits of conducting a systematic review, e.g., resolving uncertainties in a field, mitigating biases, and implementing the 3Rs principle of replacement, reduction, and refinement. He illustrated this with a recent systematic review which assessed animal-to-human translational of drugs for multiple sclerosis (Hooijmans et al., 2019).

The keynote lecture held by Dr **Cathalijn Leenaars** (Hannover Medical School, Germany) defined what a systematic review consists of, described the methodological steps used in systematic reviews, and covered the impact of methodological choices on the validity and limitations of the review outcomes. Dr Leenaars highlighted other types of reviews with value in preclinical research and explained how to select among them within the field of laboratory animal sciences (Leenaars et al., 2021). Examples of scoping (King et al., 2023), mapping (Van der Mierden et al., 2021), and umbrella (Leenaars et al., 2019) reviews showed their use and value in practice.

Prof. Dr **David Howells** (co-founder of CAMARADES) delved into the background that led to the establishment of CAMARADES (The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) by Malcolm Macleod and himself. He provided insight into the shortcomings of narrative reviews and explained why systematic reviews offer a more powerful approach. This was illustrated by examples of systematic reviews and meta-analyses in the fields of animal stroke and spinal cord injury research, which demonstrated how

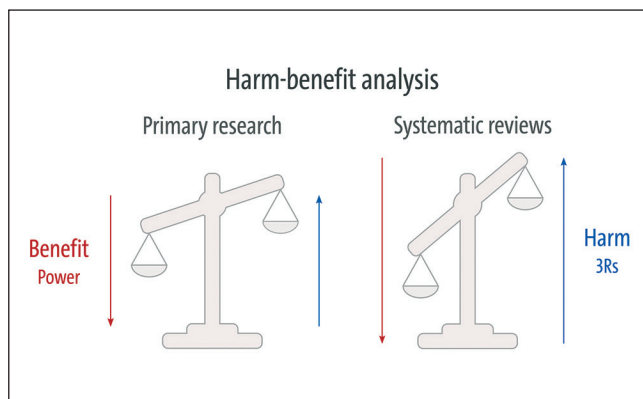


Fig. 1: Systematic reviews can enhance the harm-benefit analysis of animal studies by both increasing the benefit and reducing the harm of animal experiments



this approach provides a better understanding of the underlying biology (O'Collins et al., 2006). He concluded that taking a candidate therapy from the bench to the bedside should be based on a full and unbiased assessment of all the animal data (Howells et al., 2014) and showed how systematic review and meta-analysis can be used to design new experiments that answer critical translational questions (O'Collins et al., 2012).

Dr **Armand Mensen** from the Swiss 3Rs Competence Center (3RCC) described the different funding schemes by which the center can support researchers in conducting a systematic review of animal science, e.g., the 3RCC knowledge transfer grant and the open 3Rs science funding, aimed at making animal science more accessible and transparent.

Over the following lectures, the methodology to conduct a systematic review was covered by Dr **Marianna Rosso** (University of Zurich) and Dr Benjamin Ineichen. The methods were divided into 10 steps (Fig. 2). Lectures each covered a step of the process,

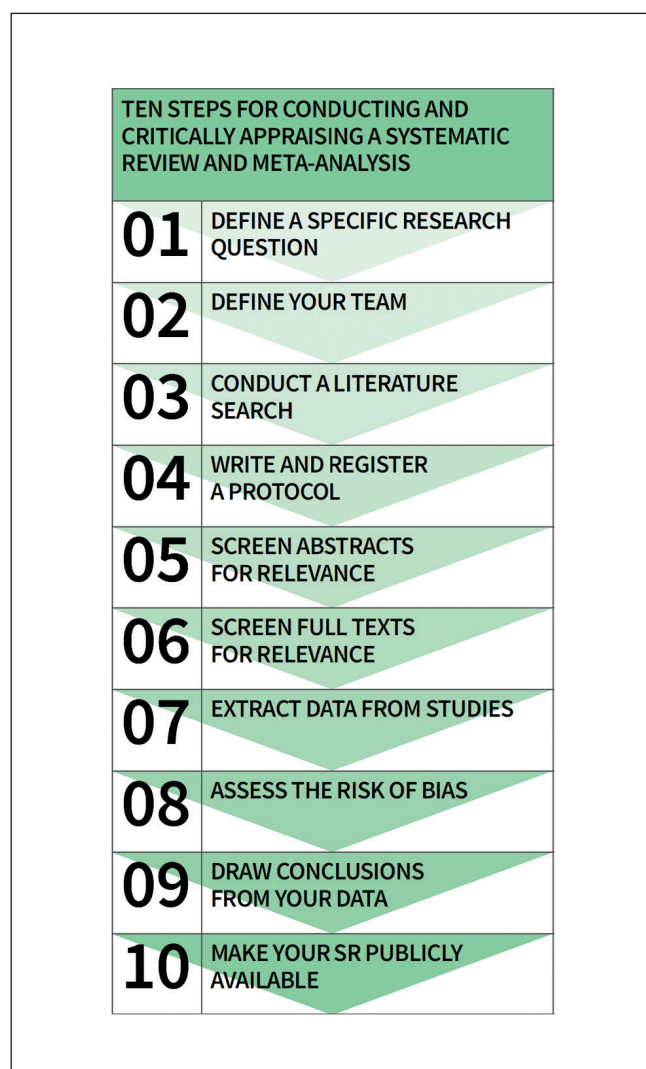


Fig. 2: The 10 steps of a systematic review and meta-analysis as used throughout the course

and after each lecture, participants were given hands-on exercises to put the taught theory into practice. During these hands-on sessions, participants worked on their own systematic reviews in the presence of the teachers.

Dr Ineichen started by outlining the PICO framework to formulate a clear research question for a systematic review, i.e., identifying the population, the intervention, the comparison, and the outcome of interest (Step 1) (Richardson et al., 1995; Eriksen and Frandsen, 2018). The participants learned about the team required to perform a systematic review and how to involve different expertise to cover all relevant aspects to ensure a rigorous systematic review, including primary researchers, systematic review methodologists, information specialists, and (bio-)statisticians (Step 2).

The second day covered the steps of conducting a search and writing a review protocol (Steps 3 and 4). Dr **Alisa Berger** (information specialist at the University of Zürich) discussed how to conduct a comprehensive and meticulously documented literature search. Her talk covered new developments in search strategies for animal studies in biomedical databases and the best approaches to building a search string, using PubMed as a working example.

The topics of writing and registering a study protocol were covered by Dr Marianna Rosso. The lecture emphasized the importance of good research practices and transparency in maintaining scientific rigor. She discussed how preregistration of a systematic review protocol can mitigate certain biases as well as bad research practices including HARKing (hypothesizing after results are known) and p-hacking (Comroy, 2019). She discussed resources to register systematic review protocols, primarily the International Prospective Register of Systematic Reviews (PROSPERO) as well as the Open Science Framework (OSF).

On day 3, Dr Ineichen taught how to screen abstracts and full texts for relevance (Steps 5 and 6) as well as how to extract pertinent data from eligible articles (Step 7). He covered the plethora of software/tools available to screen abstracts/full texts for relevance (e.g., Rayyan, SyRF or Covidence), including considerations on the strengths and weaknesses of each tool (Harrison et al., 2020; Van der Mierden et al., 2019). For data extraction, Dr Ineichen talked about commonly used tools such as Google Sheets and which types of data should be considered for extraction, and discussed the value of data transformations for subsequent meta-analysis (Chi et al., 2023). He also described potential pitfalls and their solutions including a thorough definition of metadata, the utility of pilot screening rounds, and the need to take regular breaks to avoid screening errors (Wang et al., 2020).

Dr **Rachel Heyard** (University of Zurich) discussed aspects of open and reproducible animal research, critical to the refinement domain of the 3R principle. She familiarized the participants with concepts of good research practices, including making your data and code openly available to other researchers. This included the FAIR principles to optimize the reuse of data (findable, accessible, interoperable, and reusable) (Wilkinson et al., 2016) as well as registering a publication as a preprint to ensure other researchers have early access and can avoid unnecessary duplication of animal experiments. In addition, she discussed drivers of low reproduc-



ibility and replicability in animal studies and how these challenges can be addressed (NASEM, 2019).

The fourth day of the course focused on assessing the risk of bias of studies (Step 8) and drawing conclusions from the extracted data (Step 9). Prof. Dr **Ulrike Held** (University of Zürich, Switzerland) discussed best practices to conduct a meta-analysis, i.e., a quantitative analysis of the data combining results from multiple studies (Vesterinen et al., 2014). The lecture provided insights into quantifying heterogeneity in meta-analysis, a critical aspect of drawing robust conclusions from diverse sources of data. Moreover, she explored the concept of publication bias and presented visualization techniques such as the funnel plot to identify its presence.

During the lecture on risk of bias assessment, Dr Rosso explored the concept of bias, highlighting common biases in animal research such as selection bias, performance bias, detection bias, and reporting bias. The lecture stressed the importance of these biases, which can systematically skew research results due to flaws in study design, data collection, analysis, or interpretation. She also discussed potential pitfalls in bias assessment, acknowledging subjectivity, evolution of standards over time, and challenges posed by incomplete reporting. She emphasized that bias assessment is key to interpreting systematic review results and determining the reliability and soundness of extracted data.

Simona Doneva (PhD candidate, University of Zurich), discussed potential avenues to (semi-)automate key steps of the systematic review. The talk highlighted the need for automation in systematic reviews, given that certain steps such as abstract screening and data extraction are labor-intensive (Marshall and Wallace, 2019). Training natural language processing (NLP) models to automatically classify abstracts or extract data from full texts would boost the practical implementation of systematic reviews in the field of animal research.

In the concluding remarks, Dr Ineichen stressed the importance of making a systematic review publicly available (Step 10) to mitigate publication bias at the meta-level and advance scientific knowledge, but also to inform the research community of the novel results and thus avoid unnecessary duplication of efforts.

Conclusions

The course was well received, reflected in very positive anonymized feedback gathered from all participants. The participants particularly enjoyed the balance between theory and hands-on sessions in which they could work on their own systematic reviews. In addition to enhancing participants' research skills, the summer school initiated collaborations and expanded networks of researchers interested in animal welfare. Participants will (continue to) advocate the use of systematic reviews as a means of replacing, reducing, and refining the use of animals in research. With this, we believe that systematic reviews of animal studies can make an important contribution not only to fostering evidence-based preclinical research but also to implementing animal welfare principles including the 3Rs. We are willing to share our experiences with those interested in hosting their own summer school on animal systematic reviews.

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