"A Path through the Jungle: Norecopa's 3Rs Resources" by Adrian Smith, PhD, DVM appeared in the AALAS membership magazine, Laboratory Animal Science Professional, May/June 2021, and is reprinted by permission."

A Path through the Jungle: Norecopa's 3Rs Resources

By Adrian Smith, PhD, DVM

We are living in exciting but challenging times. Never before has there been so much focus on the 3Rs, culture of care, reproducibility of animal studies, and their translatability to human medicine. The COVID-19 pandemic has brought challenges to facility management and an explosive growth in online meetings. It can seem like a hopeless task to keep up with this flood of information.

The Norwegian 3R center, Norecopa, is committed to sharing information with the global animal research community. Norecopa has gradually built a comprehensive website whose mission is to be the international one-stop-shop for links to research animal science resources (in both the lab and the field) and the 3Rs. The website currently has 9,000 pages and has 300,000 hits a year.

Online Resources

Work on the site started in 1991 with the NORINA database of alternatives to animal use in teaching and training. Information was provided for all levels, from school dissections to undergraduate teaching, to training research technicians and scientists.

NORINA and seven other databases are now embedded in the Norecopa website. We have collaborated with AWIC (the Animal Welfare Information Center at the US National Agricultural Library) for years in this process, including collecting guidelines for facility management and conducting animal experiments. The 3R Guide database embedded in the Norecopa website contains descriptions of over 400 guidelines.

With the rapid increase in online events as the pandemic developed, Norecopa's International Webinars and Meetings Calendar has grown. This comprehensive calendar includes past meetings and a list of recorded events.

Quality Research Needs Good Planning

High-quality animal research is dependent upon good planning. You can't improve a burnt cake by writing a better description of it. For this reason, Norecopa, in collaboration with British experts, has published the PREPARE guidelines for planning animal experiments.

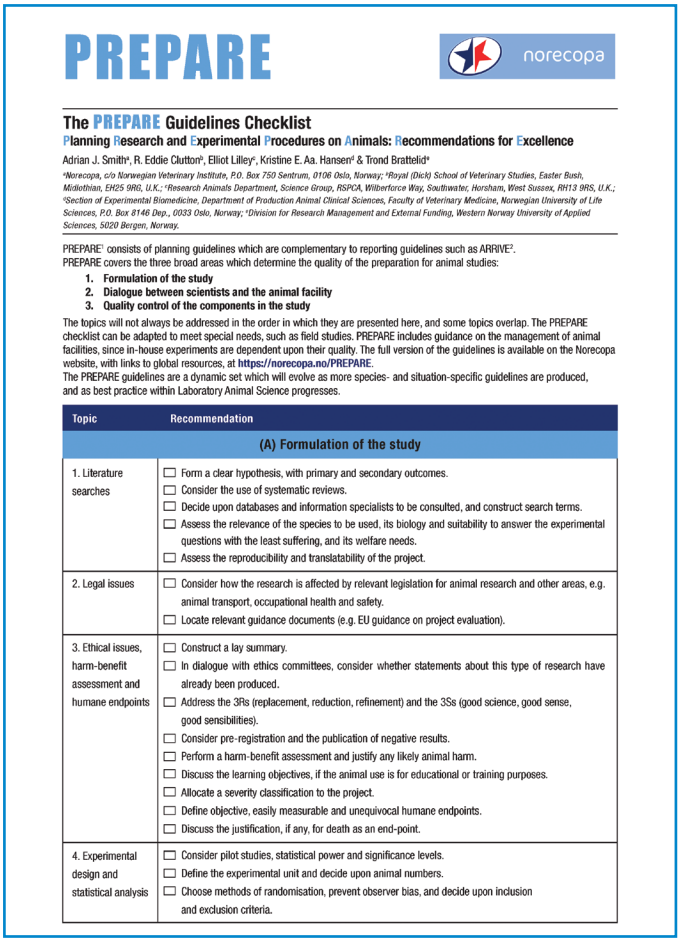
PREPARE is based upon the authors' 30 years of experience in conducting and supervising animal experiments, discussions on over 50 lab animal science courses, and lessons learned from AAALAC site visits. PREPARE consists of a 2-page checklist (Figure 1) and a website with more information on the checklist topics. The PREPARE website is updated as new resources are published. The checklist is currently available in 25 languages.

Unlike reporting guidelines, PREPARE is designed to be offered to scientists, on a voluntary basis, for use from day 1 of planning. PREPARE encourages scientists to focus on the 3Rs and become aware of all issues that can affect the research quality, and the safety and welfare of animals and staff. PREPARE emphasizes the need for close collaboration with the facility which will be hosting their work. It's no coincidence that Norecopa's motto is PREPARE for better Science.

Culture of Care

Fostering a culture of care at an animal facility is now recognized as an essential part of good management. Not only will happy animals make better science, but staff who are confident they can discuss concerns with their seniors will provide better service to the research facility. An International Culture of Care Network was established in 2016. Norecopa hosts the website for this network. There are currently members in 14 countries, and more are welcome. The website includes a Quick Start Guide for those needing a practical tips overview for improving their institution's culture. Norecopa has just published an interactive world map showing the location of network members, 3R centers and laboratory animal science associations.

Where do you find all those practical tips on technique refinements? Some tips never get published or are hidden in a paper's Materials and Methods section. Often bibliographic databases only index the title and abstract of a paper, so refinements not mentioned in these sections are often missed. Many refinements are mentioned on closed discussion forums, but



PREPARE

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The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

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PREPARE[1] consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE[2].
PREPARE covers the three broad areas which determine the quality of the preparation for animal studies:

1. **Formulation of the study**
2. **Dialogue between scientists and the animal facility**
3. **Quality control of the components in the study**

The topics will not always be addressed in the order in which they are presented here, and some topics overlap. The PREPARE checklist can be adapted to meet special needs, such as field studies. PREPARE includes guidance on the management of animal facilities, since in-house experiments are dependent upon their quality. The full version of the guidelines is available on the Norecopa website, with links to global resources, at **https://norecopa.no/PREPARE**.
The PREPARE guidelines are a dynamic set which will evolve as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

Topic	Recommendation
(A) Formulation of the study	
1. Literature searches	☐ Form a clear hypothesis, with primary and secondary outcomes. ☐ Consider the use of systematic reviews. ☐ Decide upon databases and information specialists to be consulted, and construct search terms. ☐ Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and its welfare needs. ☐ Assess the reproducibility and translatability of the project.
2. Legal issues	☐ Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. ☐ Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	☐ Construct a lay summary. ☐ In dialogue with ethics committees, consider whether statements about this type of research have already been produced. ☐ Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). ☐ Consider pre-registration and the publication of negative results. ☐ Perform a harm-benefit assessment and justify any likely animal harm. ☐ Discuss the learning objectives, if the animal use is for educational or training purposes. ☐ Allocate a severity classification to the project. ☐ Define objective, easily measurable and unequivocal humane endpoints. ☐ Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	☐ Consider pilot studies, statistical power and significance levels. ☐ Define the experimental unit and decide upon animal numbers. ☐ Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.
(B) Dialogue between scientists and the animal facility	
5. Objectives and timescale, funding and division of labour	☐ Arrange meetings with all relevant staff when early plans for the project exist. ☐ Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. ☐ Discuss and disclose all expected and potential costs. ☐ Construct a detailed plan for division of labour and expenses at all stages of the study.
6. Facility evaluation	☐ Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. ☐ Discuss staffing levels at times of extra risk.
7. Education and training	☐ Assess the current competence of staff members and the need for further education or training prior to the study.
8. Health risks, waste disposal and decontamination	☐ Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. ☐ Assess, and if necessary produce, specific guidance for all stages of the project. ☐ Discuss means for containment, decontamination, and disposal of all items in the study.
(C) Quality control of the components in the study	
9. Test substances and procedures	☐ Provide as much information as possible about test substances. ☐ Consider the feasibility and validity of test procedures and the skills needed to perform them.
10. Experimental animals	☐ Decide upon the characteristics of the animals that are essential for the study and for reporting. ☐ Avoid generation of surplus animals.
11. Quarantine and health monitoring	☐ Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel.
12. Housing and husbandry	☐ Attend to the animals' specific instincts and needs, in collaboration with expert staff. ☐ Discuss acclimatization, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing).
13. Experimental procedures	☐ Develop refined procedures for capture, immobilisation, marking, and release or rehoming. ☐ Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques.
14. Humane killing, release, reuse or rehoming	☐ Consult relevant legislation and guidelines well in advance of the study. ☐ Define primary and emergency methods for humane killing. ☐ Assess the competence of those who may have to perform these tasks.
15. Necropsy	☐ Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples.

References
1. Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattelid T. PREPARE:Guidelines for Planning Animal Research and Testing. *Laboratory Animals*, 2017, DOI: 10.1177/0023677217724823.
2. Kilkenny C, Browne WJ, Cuthill IC *et al.* Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PloS Biology*, 2010; DOI: 10.1371/journal.pbio.1000412.

Further information
https://norecopa.no/PREPARE / *post@norecopa.no* / @norecopa

Figure 1. The PREPARE checklist is reprinted with permission from Smith AJ, Clutton RE, Lilley E, Hansen KEAa, Brattelid T. 2018. PREPARE: Guidelines for planning animal research and testing. Lab Anim 52(2): 135-141. doi: 10.1177/0023677217724823
Access the PREPARE checklist: https://norecopa.no/PREPARE/prepare-checklist

they are forgotten over time. Norecopa initiated a Refinement Wiki in March 2021 for the rapid and informal publication of refinement techniques to mitigate this situation. Use of this Wiki is gradually increasing, and we encourage anyone who would like to share refinements in the Wiki to contact Norecopa.

A paper in the March 2021 issue of *JAALAS* demonstrates the importance of refinement. Rachael Labitt and colleagues show that the traditional method of scruffing mice causes bradycardia and arrhythmias persisting for an average of 4 minutes afterwards.[1] A method published by Norecopa does not have this effect. We have made a 2-minute film demonstrating the technique.

The Norecopa website also includes presentations and consensus documents from Norecopa's international consensus meetings. This is where representatives from the major stakeholders (regulators, industry, research, and animal welfare organizations) meet to identify current challenges and issue statements on how to tackle them. At these meetings, Norecopa has focused on animal groups that are not frequently discussed at mainstream lab animal science events, such as wildlife, fish, and farm animals. Collections of resources for scientists using these species are available on the website.

Please feel free to contact us if you have questions about Norecopa or would like to contribute resources to the website.

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REFERENCE

1. Labitt RN, Oxford EM, Davis AK, Butler SD, Daugherity EK. 2021. A validated smartphone-based electrocardiogram reveals severe bradyarrhythmias during immobilizing restraint in mice of both sexes and four strains. J Am Assoc Lab Anim Sci **60(2):** 1-12.

Website Resources

Norecopa: https://norecopa.no
NORINA (A Norwegian Inventory of Alternatives): https://norecopa.no/NORINA
Norecopa 3R Guide: https://norecopa.no/3r-guide
Global 3R Map: https://norecopa.no/global3R
Norecopa Webinars and Meetings Calendar: https://norecopa.no/calendar
Refined Scruffing Technique: https://norecopa.no/scruff
PREPARE: https://norecopa.no/PREPARE
International Culture of Care Network: https://norecopa.no/coc