Laboratory Animal Research

REVIEW Open Access

Guidelines for planning and conducting high-quality research and testing on animals

Adrian J. Smith

Abstract

There are important scientific, legal and ethical reasons for optimising the quality of animal research and testing. Concerns about the reproducibility and translatability of animal studies are now being voiced not only by those opposed to animal use, but also by scientists themselves.

Many of the attempts to improve reproducibility have, until recently, focused on ways in which the reporting of animal studies can be improved. Many reporting guidelines have been written. Better reporting cannot, however, improve the quality of work that has already been carried out - for this purpose better planning is required.

Planning animal studies should involve close collaboration with the animal facility where the work is to be performed, from as early a stage as possible. In this way, weaknesses in the protocol will be detected and changes can be made before it is too late. Improved planning must focus on more than the "mathematical" elements of experimental design such as randomisation, blinding and statistical methods. This should include focus on practical details such as the standard of the facility, any need for education and training, and all the factors which can improve animal welfare.

The PREPARE (*Planning Research and Experimental Procedures on Animals: Recommendations for Excellence*) checklist was developed to help scientists be more aware of all the issues which may affect their experiments. The checklist is supported by comprehensive webpages containing more information, with links to the latest resources that have been developed for each topic on the list.

Keywords: Guidelines, Planning, Reporting, Animal, Research, Testing, PREPARE, Validity, Reproducibility

Introduction

There is now widespread international acceptance for the 3R-concept (*Replacement, Reduction, Refinement* [1]) when planning research or testing which may involve the use of animals or animal tissue:

- Replacement where possible with non-animal methods
- Reduction of the number of animals to the minimum which achieves a valid result, and
- Refinement of the care and use of those animals which must be used, to maximise animal welfare and data quality.

The three Rs are now part of animal research legislation in many countries [2]. In Europe, the European Union Directive 2010/63 explicitly states that Replacement is the ultimate aim [3]. An assessment of the need to use animals at all must therefore be the first stage of the process when planning preclinical research or testing. The large range of alternatives now available is beyond the scope of this paper, but there are many sources of information of this topic (e.g. [4]).

Correspondence: adrian.smith@norecopa.no
Norecopa, P.O. Box 750 Sentrum, 0106 Oslo, Norway

If animal use is unavoidable, attention must be paid to a long list of known variables which may affect the data collected from them. Unlike test-tube ingredients, animals are complex individuals, differing in their genetic make-up, microbial composition, and behavioural responses to their environment and procedures to which they are subjected. Again, a review of all these factors is beyond the scope of this paper, but information on the effects of these variables is available (e.g. [5]).

In addition to the legal and scientific incentives, there are good ethical reasons for aiming for the highest possible quality of animal-based research and testing. This is particularly important to remember within basic research in academia, where scientists may be rewarded for the publication of new knowledge rather than for the application of their research results.

In most cases, animal research and testing is performed to learn more about another species, usually humans, rather than to shed more light on the species being used as a model. This work must, therefore, be valid, robust and translatable. As Ritskes-Hoitinga & Wever [6] remarked: 'we need a cultural change in which researchers are rewarded for producing valid and reproducible results that are relevant to patients, and for doing justice to the animals being used'. Ensuring translatability is difficult enough in itself [7], and it is totally dependent upon well-planned studies.

Quality does not come automatically: it necessitates detailed planning from day one, to take into account the effects of the internal and external parameters which affect the animals' response to a procedure. In addition, the animal facility must have a large number of routine procedures in place, both to maintain the stability of the environment and to tackle any emergencies which may arise. Many scientists who do not work on a regular basis within an animal facility are probably unaware of the number and subtlety of many of these factors. Input from the facility's veterinary staff will be central to this process.

Guidelines for planning and conducting animal-based studies help both scientists and animal facilities to discuss the issues mentioned above at an early stage, while it is still possible to make improvements in the protocol. Scientists may need to be reminded that the greatest source of variation is likely to come from the animals themselves, rather than from their treatments. Scientists may assume that the facility is dealing with these issues, but this is not always the case. The classic studies by Crabbe and coworkers, who set up standardised behavioural tests on inbred mouse strains in different laboratories simultaneously, showed how unforeseen variables can lead to significant differences in results [8, 9].

Fortunately, the need for detailed planning guidelines is becoming clearer, because the quality of animal experiments is now increasingly being criticised, not just by opponents of animal research but also by scientists themselves (e.g. [10–14]). The use of strong words such as 'research waste' and 'false results' (e.g. [15, 16]) is becoming commonplace.

Unfortunately, initiatives to solve the reproducibility crisis tend often to focus on just two of the issues: the more "mathematical" elements of experimental design, and better reporting (e.g. [17]). These issues are of course important, and include the following items, among others:

1. Publication bias (reporting only positive results)
2. Low statistical power
3. *P*-value hacking (manipulating data to obtain statistical significance)
4. HARKing *(Hypothesising After the Results are Known)*
5. Lack of randomisation and blinding

Norecopa has made a collection of literature references about these concerns [18].

However, those familiar with the workings of an animal facility can add many additional and important issues to this list, which may be less conspicuous but which are equally critical to the validity of an experiment. These may be grouped into:

1. Artefacts caused by internal factors such as genetic diversity and subclinical infections
2. Artefacts caused by external effects such as transport, cage conditions, re-grouping of animals, food deprivation and the procedure itself
3. The need for contingency plans to reduce or avoid these and other risks in the facility

Reporting does not improve the standard of experiments

Good reporting is of course important, to allow readers to evaluate the scientific quality of the publication and the strength of the conclusions drawn by the authors. Insistence on better reporting is not new. When Laboratory Animal Science as we know it today was under development in the second half of the last century, focus was placed at an early stage on the low standard of reporting in the scientific literature. In a classic paper, Jane Smith and colleagues [19] examined the descriptions of laboratory animals, and the procedures for which they were used, in 149 scientific papers published in 8 major journals from 1990 to 1991. The percentages of papers not reporting basic details about the animals were alarmingly high (e.g. sex: 28%; age: 52%; weight: 71%; source: 53%), and 30% of the papers did not mention how many animals were used. The percentages were even higher for environmental factors such as room

temperature (72%), photoperiod (72%), relative humidity (89%) and the number of animals per cage (73%).

Many reporting guidelines have been written since the 1980s, to encourage improvements. These include both general guidance (e.g. [20–24]) and guidelines written for specific types of experiment (e.g. [25–28]).

It is vitally important to remember that better reporting of an experiment which has already been performed cannot improve the quality of that experiment. A good salesman may manage to sell more burnt cakes if he describes them well (and if he is a good psychologist), but they will still be burnt and they will not taste better. To improve a cake, one must go back to the kitchen and modify the ingredients and/or the baking conditions. In the case of animal studies, just as in the kitchen, the quality of the result is dependent upon planning and conducting, not reporting.

This has been well demonstrated by the way in which the ARRIVE (*Animal Research: Reporting of* In Vivo *Experiments*) guidelines for reporting animal experiments [23] have been received and implemented. A new version of ARRIVE was developed in 2019 [29], because, as the authors point out, despite endorsement by more than a thousand journals, only a small number of these journals actively enforce compliance. Indeed, a Swiss study revealed that 51% of researchers using journals that had endorsed ARRIVE had even never heard of them [30]. The authors of ARRIVE concluded that most journals are unlikely to be able to provide the resources needed to ensure compliance with all the items on the original checklist. The new version of the ARRIVE guidelines has a shorter checklist of 'essential' items, to try and increase compliance. This situation demonstrates clearly how important the *planning* stage is for the quality of scientific papers.

Scientists should contact the animal facility as soon as they have concrete plans of conducting animal studies. Collaboration between scientists and facility staff will be needed to discuss all stages of the study, up to and including the end of the study which involves depopulation, decontamination and waste disposal. An essential part of this process is attention to the needs of the facility staff. This includes, among other things, their education and training, personal protection, their workload, and means of ensuring adequate staffing levels at all times during the study.

Preparation for preclinical studies: a modern definition of the 3Rs

The concept of the three Rs *(Replacement, Reduction and Refinement)* developed by Russell and Burch over 60 years ago [1] was written in an era when the most pressing need was to reduce the inhumanity of animal experiments. Technology at that time did not offer the same potential to replace such experiments as is available today - neither was there so much focus on reducing animal numbers by more sophisticated experimental design.

So today, preparation for robust, valid and humane preclinical studies should go beyond a mere search for more humane methods, using more contemporary definitions of the three Rs [31]:

- Replacement is not just the use of methods which achieve a given purpose without procedures on animals, but also about total avoidance of animal use (Non-Animal Models, NAMs) by innovative approaches to scientific problems, for example by studies directly on human tissue
- Reduction is about obtaining comparable information from fewer animals, or for obtaining more information from the same number of animals. Today, reduction also focuses on optimalisation of experimental design so that *experiments are robust and reproducible*
- Refinement methods minimise pain, suffering or distress, but also improve animals' well-being, since modern research demonstrates that this affects the quality of the data collected from the animals. Modern technology can be harnessed to refine the methods and equipment we use on animals.

Animals that are in harmony with their surroundings will provide more reliable scientific data in an experiment, because the parameters measured will reflect the treatment they are given, rather than being affected by stress. It is indeed true that 'happy animals give better science' [32, 33].

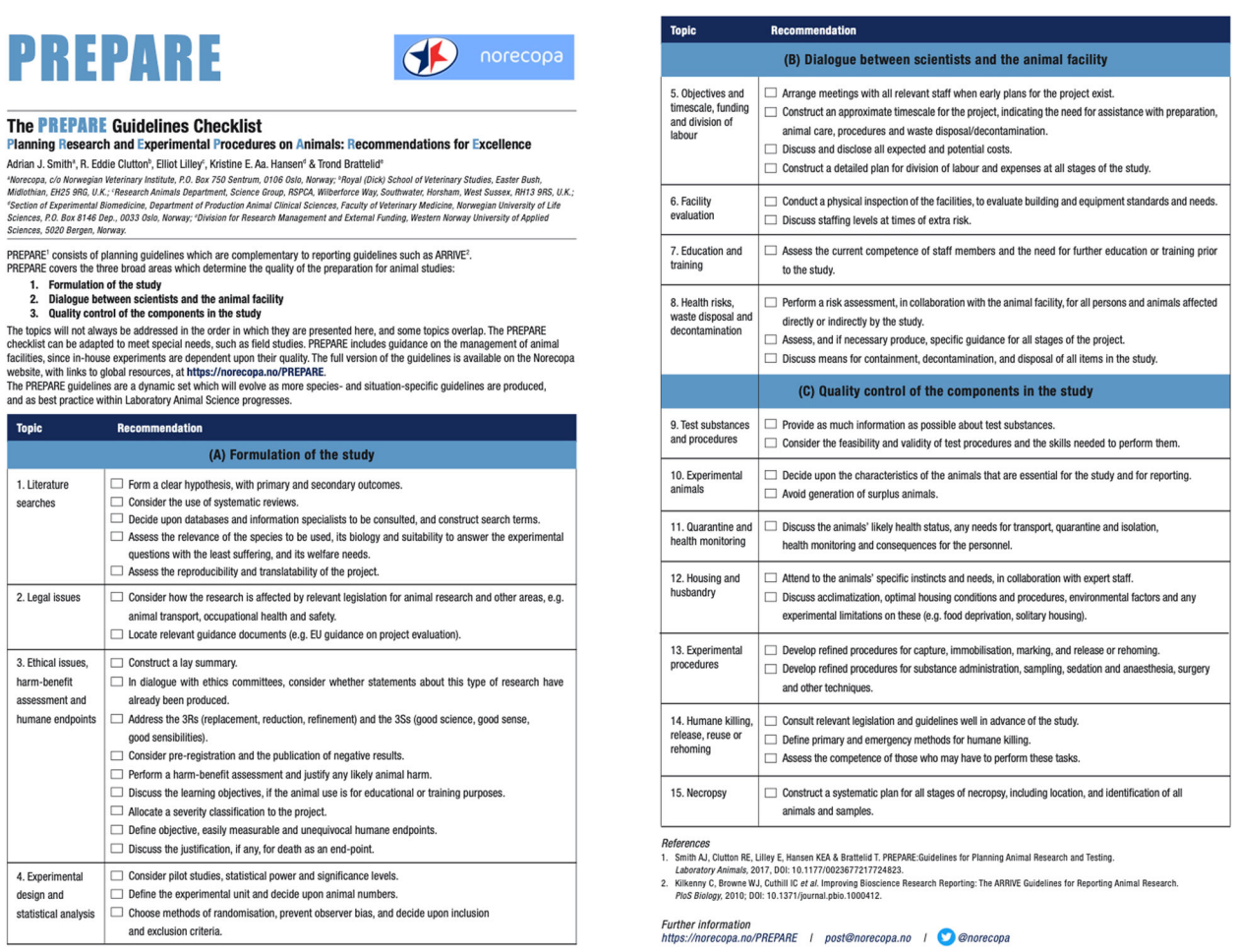
For these reasons, scientists must be given comprehensive guidelines for planning any experiments which may involve the use of animals, or material taken from animals.

The PREPARE guidelines

Based on the authors' experiences over the past 30 years in designing and supervising animal experiments, comprehensive guidelines for planning animal studies have been constructed, called PREPARE (*Planning Research and Experimental Procedures on Animals: Recommendations for Excellence*) [34].

PREPARE contains a checklist, which serves as a reminder of items that should be considered before and during the study, see Fig. 1. This checklist is available in over 20 languages.

Many of these items will need their own sets of checklists or standard operating procedures, in the same way that pilots, however experienced, use many checklists, even on routine flights, before, during and after the flight. Many of these checklists will be produced by the animal



PREPARE

norecopa

The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Adrian J. Smith[a], R. Eddie Clutton[b], Elliot Lilley[c], Kristine E. Aa. Hansen[d] & Trond Brattelid[e]

[a]Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750 Sentrum, 0106 Oslo, Norway; [b]Royal (Dick) School of Veterinary Studies, Easter Bush, Midlothian, EH25 9RG, U.K.; [c]Research Animals Department, Science Group, RSPCA, Wilberforce Way, Southwater, Horsham, West Sussex, RH13 9RS, U.K.; [d]Section of Experimental Biomedicine, Department of Production Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, P.O. Box 8146 Dep., 0033 Oslo, Norway; [e]Division for Research Management and External Funding, Western Norway University of Applied Sciences, 5020 Bergen, Norway.

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

Fig. 1 The PREPARE checklist (available at https://norecopa.no/PREPARE/prepare-checklist). From Smith, AJ, Clutton, RE, Lilley, E, Hansen KEAa, Brattelid, T. PREPARE: Guidelines for planning animal research and testing. Laboratory Animals, 2018;52:135–141. DOI: https://doi.org/10.1177/0023677217724823. Published under Open Access, Creative Commons licence CC BY-NC 4.0

facility itself. Scientists should, however, check that these are in place, and discuss their contents with the facility.

Importantly, and unlike many reporting guidelines, the PREPARE checklist is supported by a website which provides more information on each of the 15 main topics on the checklist (https://norecopa.no/PREPARE). The website gives more complete guidance in the form of text and links to quality guidelines and scientific papers. This website is continually updated as new knowledge develops.

The PREPARE guidelines contain, of course, many of the elements found in reporting guidelines. However, PREPARE contains additional material about issues that can have dramatic effects on the scientific validity of the research, as well as on health and safety, and animal welfare.

Contingency plans and resources

Human nature is such that we tend to believe that accidents only happen to others. If this belief is followed in an animal facility, it will not only put the outcome of a scientific study at risk, but it will also endanger the health and lives of both the animals and personnel who are directly or indirectly involved in the study. As indicated above, it is important to ensure the quality of the whole process from obtaining the animals to disposal of waste and decontamination after the study.

A competent animal facility is one that *"hopes for the best but is prepared for the worst"*. Facilities with comprehensive and realistic contingency plans will be well placed to tackle disasters, including lockdown situations in connection with a pandemic. There are many resources available that describe the general principles involved, but these must be tailored to the local conditions at each facility. Building a contingency plan from scratch is a time-consuming affair, but it is an excellent insurance policy for the day when a threatening situation arises. Those lacking such a plan should begin with a risk assessment of the facility and its activities, and start

by writing contingency plans for the most important of these scenarios.

In its simplest terms, risk assessment is the consequence of a threat multiplied by the likelihood of it occurring. The consequences of the threat include the level of tolerance of the event occurring, which may be anything from "totally unacceptable" to "acceptable within certain limits". Assessments should be performed at several levels, since threats and their consequences may differ, depending upon where and when they occur, for example:

- at the facility level (e.g. the consequences of flooding or fire)
- at the room level (e.g. the consequences of power outages to vital equipment)
- in connection with specific types of research (e.g. risk of human infection)

It is wise to construct a contingency plan based upon the assumption that 'what can go wrong will go wrong at some time' [35], and that this will happen when it is least convenient, for example during public holidays when staffing levels may be low.

Clearly, both the design of animal studies and the production of contingency plans must involve close collaboration between management, scientists and technical staff, including external suppliers of equipment and services.

The Covid-19 pandemic has demonstrated the importance of being adequately prepared. Animal facilities have had to quickly write contingency plans to tackle situations which were barely imaginable before the outbreak. This work has demanded enormous time and energy, at the expense of conducting research, and it has left many facilities with the unpleasant task of having to euthanise large numbers of healthy animals. Clearly, it is easier to tackle these situations, however improbable they may seem, if the majority of the issues which may arise have already been discussed, and plans made to tackle them.

At the time of writing, some specific advice on contingency plans for the Covid-19 pandemic is beginning to emerge, and existing advice on disaster planning is being re-examined (see [36]).

Collaboration between scientists and animal care staff

There are many good reasons for early and close collaboration between scientists and the staff at the animal facility where they hope to carry out the work. This collaboration should include dialogue with the animal carers and technicians, not just with the managers. Some of the reasons include the following:

- the staff have a moral right to know what will happen to animals in their care.
- they will be more motivated to look for ways of refining the study. This will improve both animal welfare and the scientific quality, including reliability of the data being collected from the animals.
- the animal care staff know the possibilities, and the limitations, of the animal facility best. They are less likely to play limitations down for fear of the study being transferred to another facility.
- they often possess a large range of practical skills and are good at lateral thinking from one study to another - they may be able to suggest a refinement which they have already seen in another species.
- they know the animals best
- the animals know them best
- lack of involvement of the animal care staff creates anxiety, depression and opposition to animal research, as well as limiting creativity which might improve the experiments

A mutually respectful dialogue between technical and academic staff will also help resolve issues quickly which may otherwise cause disagreements later, such as the division of labour and responsibilities all stages of the study. It will also help to avoid the loss of important data due to misunderstandings about who was to collect it.

Culture of care and challenge

To facilitate this dialogue, steps should be taken to foster a culture of care among all members of the staff and research teams. This is actively encouraged in European legislation [3]. Animal research will inevitably, from time to time, involve studies where sentient creatures exhibit pain, suffering and distress. It is therefore vital to consider the mental health of those caring for these animals or observing this, to avoid compassion fatigue. In Europe, an International Culture of Care network has been established, to share experiences in implementing such a culture [37].

Closely related to a culture of care is the concept of a Culture of Challenge [38]. This is all about 'looking for the acceptable, rather than choosing the accepted'. Comments such as "we have always done it that way" or "we do it as often as necessary" should automatically start a discussion about how to change these habits.

Conclusion

It can be hoped that the current focus on poor reproducibility in animal studies can be turned into an initiative to ensure better planning of all stages, rather than focusing on improving reporting. Otherwise, we are in danger of wasting time, discussing the quality of the lock on the door of the stable from which the horse has already escaped [39].

Acknowledgements
The author acknowledges the contributions of the co-authors of the PREPARE guidelines and other colleagues within Laboratory Animal Science over many years, which led to the development of the PREPARE guidelines and many of the principles mentioned in this paper.

Author's contributions
Adrian Smith is sole author and contributor to this paper. The author read and approved the final manuscript.

Authors' information
Adrian Smith is Secretary of Norecopa, which is affiliated to the Norwegian Veterinary Institute. The views expressed in this paper are his own, and not necessarily those of Norecopa or the Veterinary Institute.

Funding
The work of Norecopa has been supported by a large number of sponsors (https://norecopa.no/sponsors). No specific funding was obtained for the production of this paper. The author thanks the Universities Federation of Animal Welfare (UFAW), U.K., for funding the open access publication of the paper from which Fig. 1 is taken.

Availability of data and materials
This review paper does not include original data. Figure 1 is from a previous paper, published under Open Access, Creative Commons licence CC BY-NC 4.0.

Competing interests
Adrian Smith is lead author of the PREPARE guidelines and has editorial responsibility for creation and updating of the Norecopa website (https://norecopa.no), both of which are cited several times in this paper. He has no other competing interests.

Received: 20 May 2020 Accepted: 25 June 2020
Published online: 10 July 2020

References

1. Russell WMS, Burch RL. The principles of humane experimental technique. London: Methuen; 1959.
2. Javier G. Laboratory animals: regulations and recommendations for the care and use of animals in research. 2nd ed. ISBN 9780128498804. London: Academic Press; 2018.
3. European Commission. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. 2010. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF. Accessed 15 May 2020.
4. EURL-ECVAM. Finding information on alternative methods. 2020 https://ec.europa.eu/jrc/en/eurl/ecvam/knowledge-sharing-3rs/finding-information-alternative-methods. Accessed 15 May 2020.
5. Norecopa. Housing and husbandry. 2020a. https://norecopa.no/prepare/12-housing-and-husbandry. Accessed 15 May 2020.
6. Ritskes-Hoitinga M, Wever K. Improving the conduct, reporting, and appraisal of animal research. BMJ. 2018. https://doi.org/10.1136/bmj.j4935.
7. Pound P, Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. J Transl Med. 2018. https://doi.org/10.1186/s12967-018-1678-1.
8. Crabbe JC, Wahlsten D, Dudek BC. Genetics of mouse behavior: interactions with laboratory environment. Science. 1999;284:1670–2.
9. Wahlsten D, Metten P, Phillips TJ, Boehm LL II, Burkhart-Kasch C, Dorow J, et al. Different data from different labs: Lessons from studies of gene-environment interaction. J Neurobiol. 2003. https://doi.org/10.1002/neu.10173.
10. Avey MT, Moher D, Sullivan KJ, Fergusson D, Griffin G, Grimshaw JM, et al. The devil is in the details: incomplete reporting in preclinical animal research. PLoS One. 2016;11:e0166733. https://doi.org/10.1371/journal.pone.0166733.
11. Baker M. 1,500 scientists lift the lid on reproducibility. Nature. 2016. https://doi.org/10.1038/533452a.
12. Bradbury AG, Eddleston M, Clutton RE. Pain management in pigs undergoing experimental surgery; a literature review. Br J Anaesthesiol. 2016. https://doi.org/10.1093/bja/aev301.
13. Enserink M. Sloppy reporting on animal studies proves hard to change. Science. 2017. https://doi.org/10.1126/science.357.6358.1337.
14. Skibba R. Swiss survey highlights potential flaws in animal studies. Nature. 2016. https://doi.org/10.1038/nature.2016.21093.
15. Ioannidis JPA. Why Most published research findings are false. PLoS Med. 2005. https://doi.org/10.1371/journal.pmed.0020124.
16. Macleod MR. Biomedical research: increasing value, reducing waste. Lancet. 2014;383. https://doi.org/10.1016/S0140-6736(13)62329-6.
17. Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, et al. A manifesto for reproducible science. Nat Hum Behav. 2017. https://doi.org/10.1038/s41562-016-0021.
18. Norecopa. Experimental design and reporting: concerns. 2020b. https://norecopa.no/concerns. Accessed 15 May 2020.
19. Smith JA, Birke L, Sadler D. Reporting animal use in scientific papers. Lab Anim. 1997. https://doi.org/10.1258/002367797780596176.
20. Brattelid T, Smith AJ. Guidelines for reporting the results of experiments on fish. Lab Anim. 2000. https://doi.org/10.1258/002367700780457590.
21. Ellery AW. Guidelines for specification of animals and husbandry methods when reporting the results of animal experiments. Working Committee for the Biological Characterization of Laboratory Animals / GV-SOLAS. Lab Anim. 1985. https://doi.org/10.1258/002367785780942714.
22. Hooijmans CR, Leenaars M, Ritskes-Hoitinga M. A gold standard publication checklist to improve the quality of animal studies, to fully integrate the three Rs, and to make systematic reviews more feasible. Altern Lab Anim. 2010. https://doi.org/10.1177/026119291003800208.
23. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol. 2010. https://doi.org/10.1371/journal.pbio.1000412.
24. Öbrink KJ, Rehbinder C. Animal definition: a necessity for the validity of animal experiments? Lab Anim. 2000. https://doi.org/10.1258/002367700780457608.
25. Bramhall M, Flórez-Vargas O, Stevens R, Brass A, Cruickshank S. Quality of methods reporting in animal models of colitis. Inflamm Bowel Dis. 2015. https://doi.org/10.1097/MIB.0000000000000369.
26. Guidelines for the treatment of animals in behavioural research and teaching. Anim Behav. 2020. https://doi.org/10.1016/j.anbehav.2019.11.002.
27. Smith MM, Clarke EC, Little CB. Considerations for the design and execution of protocols for animal research and treatment to improve reproducibility and standardization: DEPART well-prepared and ARRIVE safely. Osteoarthr Cartil. 2017. https://doi.org/10.1016/j.joca.2016.10.016.
28. STAIR Consensus Conferences. 2017. http://www.thestair.org/. Accessed 15 May 2020.
29. Du Sert NP, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al. The ARRIVE guidelines 2019: updated guidelines for reporting animal research. bioRxiv. 2019. https://doi.org/10.1101/703181.
30. Reichlin TS, Vogt L, Wurbel H. The researchers' view of scientific rigor-survey on the conduct and reporting of in vivo research. PLoS One. 2016. https://doi.org/10.1371/journal.pone.0165999.
31. Norecopa. The three R's. 2020c. https://norecopa.no/alternatives/the-three-rs. Accessed 15 May 2020.
32. NC3Rs. Training techniques for less stressed laboratory rodents. 2019. https://www.nc3rs.org.uk/news/highlights-2019-nc3rsiat-animal-technicians-symposium#rodenttraining. Accessed 18 May 2020.
33. Poole T. Happy animals make good science. Lab Anim. 1997. https://doi.org/10.1258/002367797780600198.
34. Smith AJ, Clutton RE, Lilley E, Hansen KEA, Brattelid T. PREPARE: guidelines for planning animal research and testing. Lab Anim. 2018a. https://doi.org/10.1177/0023677217724823.
35. Murphy's Law. Wikipedia. 2020. https://en.wikipedia.org/wiki/Murphy%27s_law. Accessed 15 May 2020.
36. Norecopa. Be PREPARED. 2020d. https://norecopa.no/be-prepared. Accessed 15 May 2020.
37. Norecopa (2020e): Culture of care. https://norecopa.no/CoC. Accessed 15 May 2020.
38. Louhimies S. Refinement facilitated by the Culture of Care. In: ALTEX Proceedings of the EUSAAT 2015-Linz 2005 Congress, 20-23 September, Linz, vol. 4; 2015. p. 154. http://eusaat-congress.eu/images/2015/Abstractbook_EUSAAT_2015_Linz_2015.pdf. Accessed 15 May 2020.
39. Smith AJ, Clutton RE, Lilley E, Hansen KEA, Brattelid T. Improving animal research: PREPARE before you ARRIVE. BMJ. 2018b. https://doi.org/10.1136/bmj.k760.

Publisher's Note