ESLAV-ECLAM-AAALAC-SECAL Conference, Barcelona, 15-16 October 2018

PREPARE before you ARRIVE:

How to plan animal experiments

norecopa.no/Barcelona

Adrian Smith, Eddie Clutton, Elliot Lilley, Kristine Hansen & Trond Brattelid

adrian.smith@norecopa.no

norecopa.no

norecopa.no

70,000 euros

Organisations of relevance to animal research

Organisations within Laboratory Animal Science

AAALAC International (Association for Assessment and Accreditation of Laboratory Animal Care International)
AALAS (American Association for Laboratory Animal Science)
ACLAM (American College of Laboratory Animal Medicine)
AniMatch (an online sharing platform for the exchange of organs and tissues)
ARSAL (Asociatia Româna pentru Stiinta Animalelor de Laborator; Romanian Laboratory Animal Science Association)
ASLAP (American Society of Laboratory Animal Practitioners)

7,600 webpages
80,000 references
22,000 unique links
160,00 pageviews/year

International consensus meetings

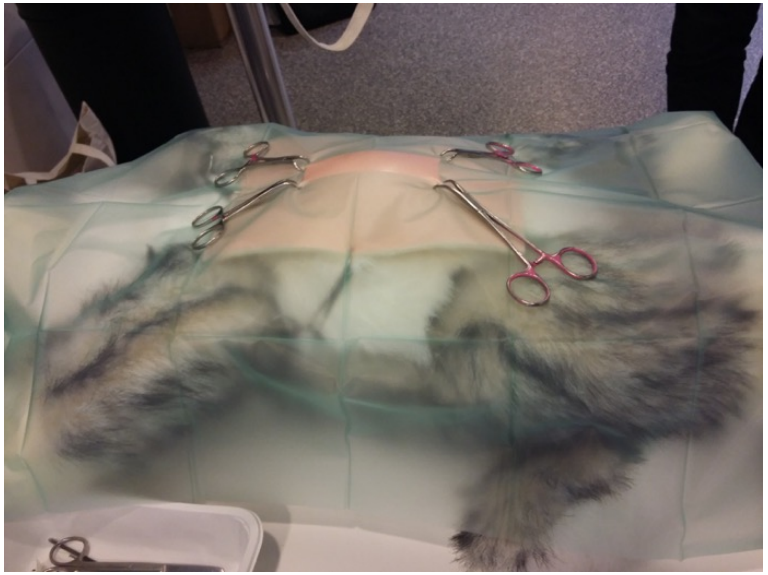
Harmonisation of the Care and Use of:

- *Fish (2005)*
- *Wildlife (2008)*
- *Fish (2009)*
- *Agricultural animals (2012)*
- *Wildlife (2017)*

https://norecopa.no/meetings

All presentations and consensus statements are on the internet: ***a lasting resource***

Laura-Kim Schüller, Veterinary School, Berlin



Rikke Langebæk, University of Copenhagen

Workshop 11. april i Oslo
norecopa.no/education-training/homemade-educational-materials

http://bitly.com/scruff-technique

http://bitly.com/scruff-technique

An useful additional (but largely unknown) tool…
Carol M. Newton (1925-2014)


National Library of Medicine

The three S's

- *Good Science*
- *Good Sense*
- *Good Sensibilities*

norecopa.no/3S

Carol M Newton, quoted in Rowsell HC (1977): The Ethics of Biomedical Experimentation in The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing pp. 267-281, National Academy of Sciences, Washington, D.C., ISBN 0-309-02603-2.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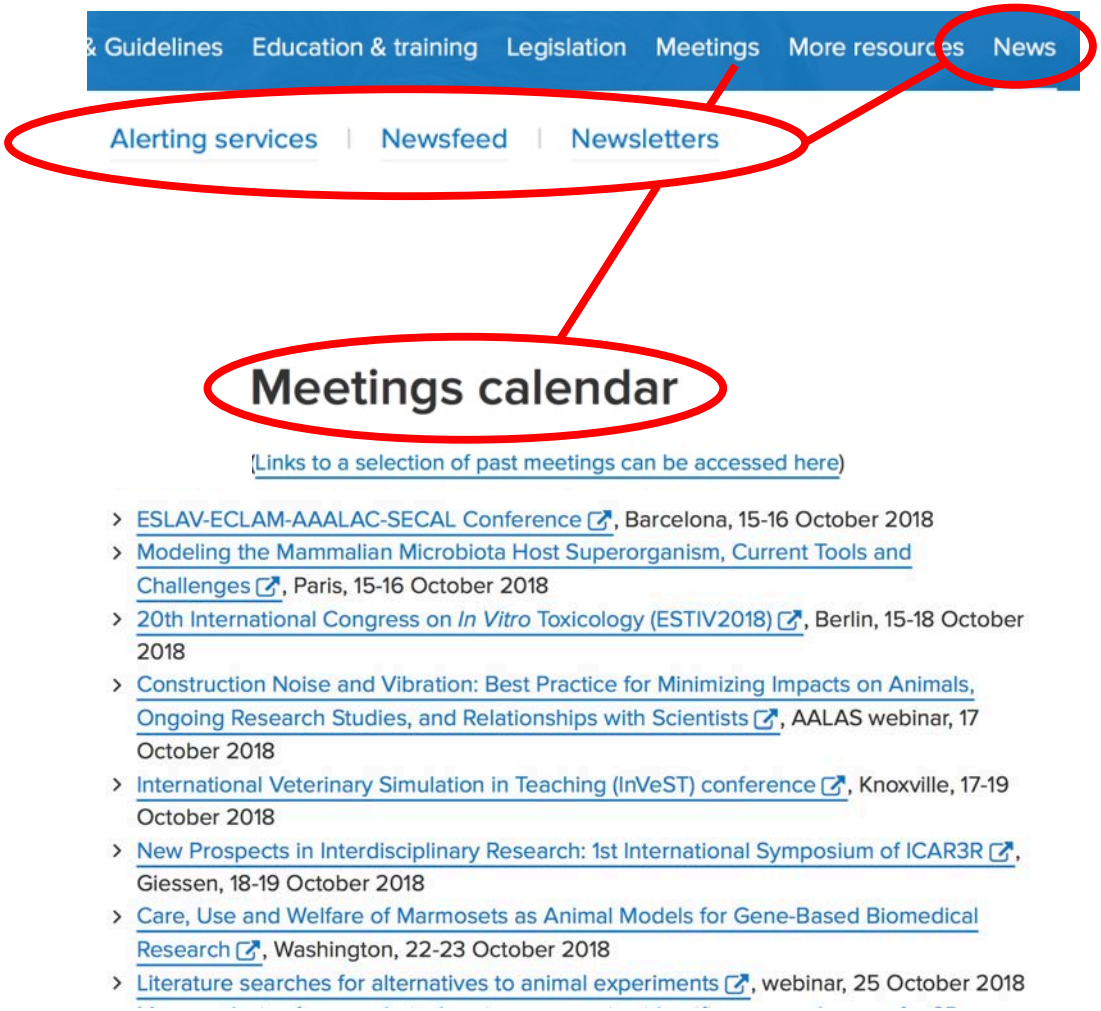
& Guidelines
Education & training
Legislation
Meetings
More resources
News
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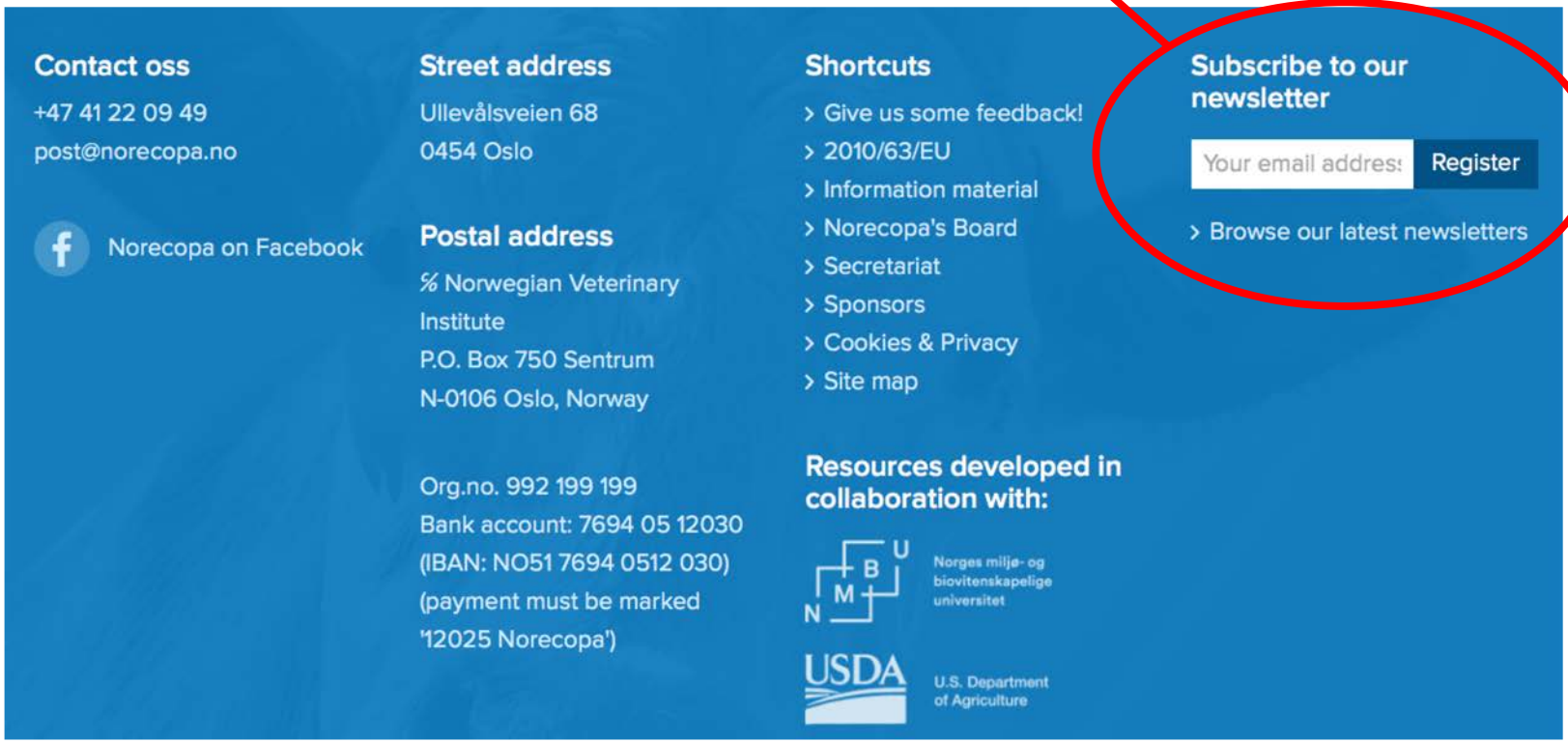
Meetings calendar
(Links to a selection of past meetings can be accessed here)
ESLAV-ECLAM-AAALAC-SECAL Conference, Barcelona, 15-16 October 2018
Modeling the Mammalian Microbiota Host Superorganism, Current Tools and Challenges, Paris, 15-16 October 2018
20th International Congress on In Vitro Toxicology (ESTIV2018), Berlin, 15-18 October 2018
Construction Noise and Vibration: Best Practice for Minimizing Impacts on Animals, Ongoing Research Studies, and Relationships with Scientists, AALAS webinar, 17 October 2018
International Veterinary Simulation in Teaching (InVeST) conference, Knoxville, 17-19 October 2018
New Prospects in Interdisciplinary Research: 1st International Symposium of ICAR3R, Giessen, 18-19 October 2018
Care, Use and Welfare of Marmosets as Animal Models for Gene-Based Biomedical Research, Washington, 22-23 October 2018
Literature searches for alternatives to animal experiments, webinar, 25 October 2018

Norecopa's English-language newsletters



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News & Comment > News > 2017 > May > Article

NATURE | NEWS

Swiss survey highlights potential flaws in animal studies

Poor experimental design and statistical analysis could contribute to widespread problems in reproducing preclinical animal experiments.

Ramin Skibba

20 December 2016

Pain management in pigs undergoing experimental surgery; a literature review (2012–4)

A. G. Bradbury, M. Eddleston, R. E. Clutton

Br J Anaesth (2016) 116 (1): 37-45. **DOI:** https://doi.org/10.1093/bja/aev301

Published: 03 October 2015

...gs with analgesic properties, but only 87/233 (37%) described postoperative analgesia. No article provided justification for the analgesic chosen, despite the lack of guidelines for analgesia in porcine surgical models and the lack of formal studies on this subject. Postoperative pain assessment was reported in only 23/233 (10%) articles. It was found that the reporting of postoperative pain management in the studies was remarkably low, reflecting either under-reporting or under-use. Analgesic description, when given, was frequently too limited to enable reproducibility. Development of a

nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audi

Archive > Volume 533 > Issue 7604 > News Feature > Article

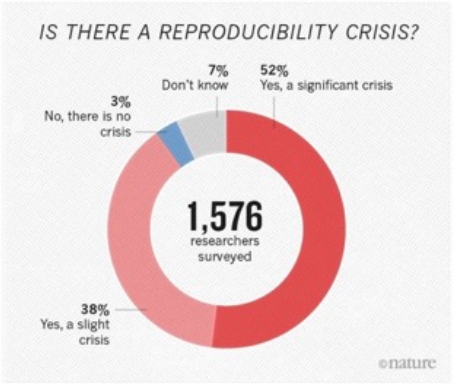
NATURE | NEWS FEATURE

1,500 scientists lift the lid on reproducibility

Survey sheds light on the 'crisis' rocking research.

Monya Baker

25 May 2016 | Corrected: 28 July 2016



More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments. Those are some of the telling figures that emerged from *Nature*'s survey of 1,576 researchers who took a brief online questionnaire on reproducibility in research.

Why is it taking so long to improve reproducibility?

Berti & Cima 1955, quoted in Öbrink and Rehbinder

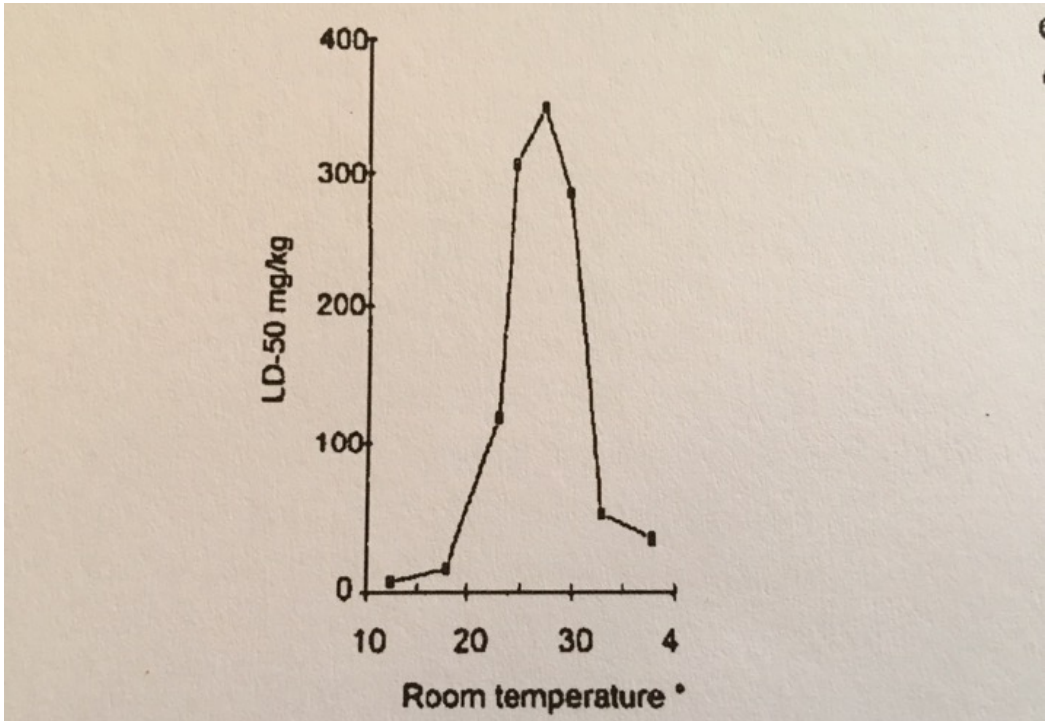


Fig 7 Influence of room temperature on LD-50 of the drug Chlorpromazine in mouse

Hurni 1969, quoted in Öbrink and Rehbinder

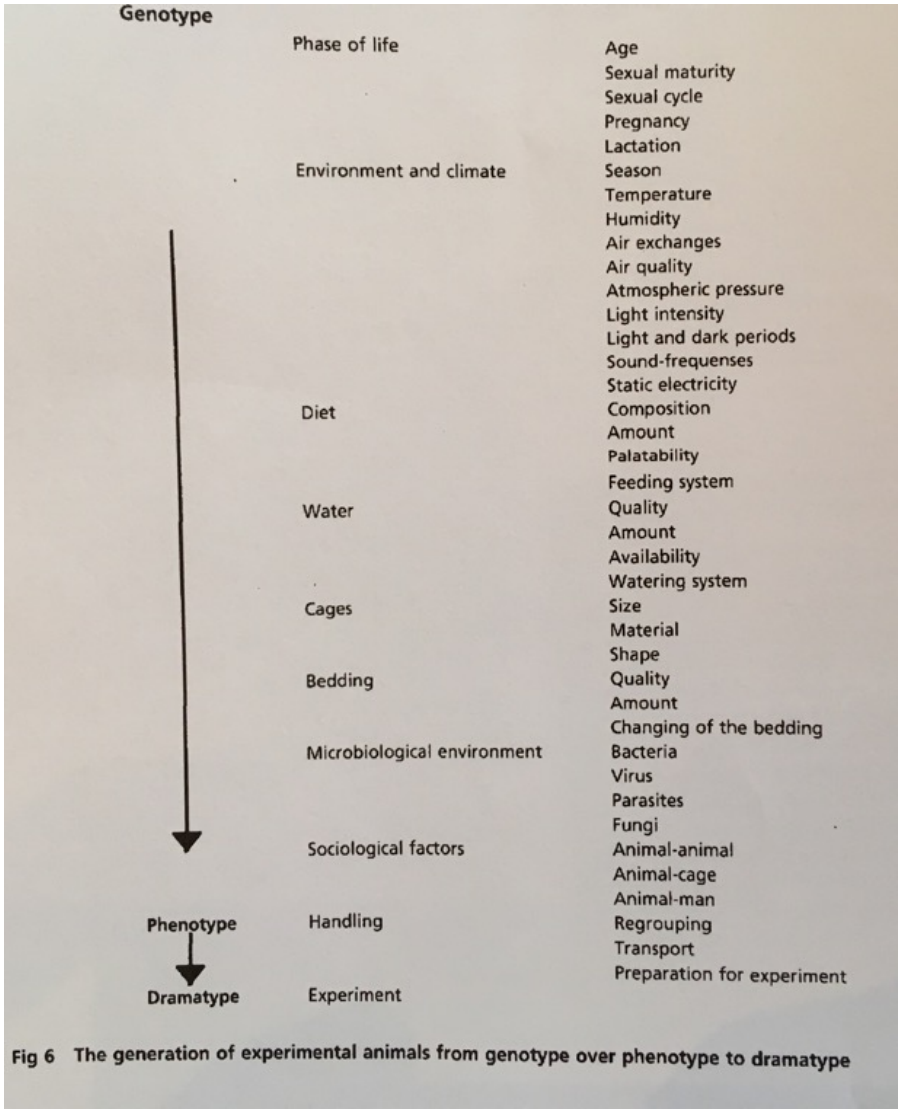


Fig 6 The generation of experimental animals from genotype over phenotype to dramatype

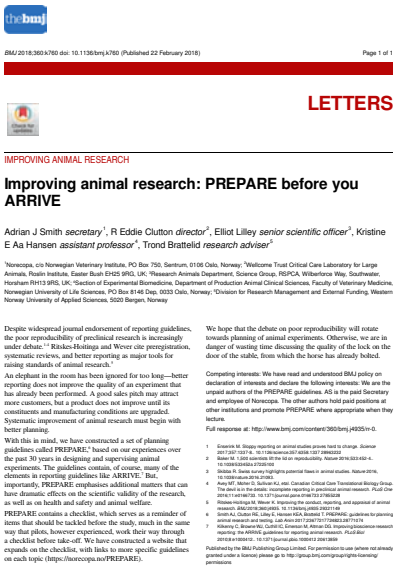
There are many guidelines for *reporting* animal studies, e.g.

- GV-Solas, 1985
- Öbrink & Waller, 1996
- Jane Smith *et al.*, 1997
- Öbrink & Rehbinder: Animal definition: a necessity for the validity of animal experiments? *Laboratory Animals,* 2000
- ARRIVE Guidelines, 2010 (Kilkenny *et al.*, NC3Rs)
- Gold Standard Publication Checklist, 2010 (SYRCLE)
- Institute for Laboratory Animal Research, NRC, 2011
- Instructions to authors, in many journals

  e.g. Nature's Reporting Checklist

www.pixcove.com

Are we wasting time discussing the quality of the lock on the door of the stable from which the horse has already bolted?



thebmj

BMJ 2018;360:k760 doi: 10.1136/bmj.k760 (Published 22 February 2018) Page 1 of 1

LETTERS

IMPROVING ANIMAL RESEARCH

Improving animal research: PREPARE before you ARRIVE

Adrian J Smith *secretary*[1], R Eddie Clutton *director*[2], Elliot Lilley *senior scientific officer*[3], Kristine E Aa Hansen *assistant professor*[4], Trond Brattelid *research adviser*[5]

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Despite widespread journal endorsement of reporting guidelines, the poor reproducibility of preclinical research is increasingly under debate.[1,2] Ritskes-Hoitinga and Wever cite preregistration, systematic reviews, and better reporting as major tools for raising standards of animal research.[3]

An elephant in the room has been ignored for too long—better reporting does not improve the quality of an experiment that has already been performed. A good sales pitch may attract more customers, but a product does not improve until its constituents and manufacturing conditions are upgraded. Systematic improvement of animal research must begin with better planning.

With this in mind, we have constructed a set of planning guidelines called PREPARE,[4] based on our experiences over the past 30 years in designing and supervising animal experiments. The guidelines contain, of course, many of the elements in reporting guidelines like ARRIVE.[5] But, importantly, PREPARE emphasises additional matters that can have dramatic effects on the scientific validity of the research, as well as on health and safety and animal welfare.

PREPARE contains a checklist, which serves as a reminder of items that should be tackled before the study, much in the same way that pilots, however experienced, work their way through a checklist before take-off. We have constructed a website that expands on the checklist, with links to more specific guidelines on each topic (https://norecopa.no/PREPARE).

We hope that the debate on poor reproducibility will rotate towards planning of animal experiments. 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 bolted.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: We are the unpaid authors of the PREPARE guidelines. AS is the paid Secretary and employee of Norecopa. The other authors hold paid positions at other institutions and promote PREPARE where appropriate when they lecture.

Full response at: http://www.bmj.com/content/360/bmj.j4925/rr-0.

1 Errington M. Sloppy reporting on animal studies proves hard to change. *Science* 2017;357:1317-8. 10.1126/science.357.6358.1317 28963232

2 Baker M. 1,500 scientists lift the lid on reproducibility. *Nature* 2016;533:452–4. 10.1038/533452a 27225100

3 Ritskes-Hoitinga M, Wever K. Improving the conduct, reporting, and appraisal of animal research. *BMJ* 2018;360:j4935. 10.1136/bmj.j4935 29367198

4 Avey MT, Moher D, Sullivan KJ, et al; Canadian Critical Care Translational Biology Group. The devil is in the details: incomplete reporting in preclinical animal research. *PLoS One* 2016;11:e0166733. 10.1371/journal.pone.0166733 27902748

5 Ritskes-Hoitinga M, Wever K. Improving the conduct, reporting, and appraisal of animal research. *BMJ* 2018;360:j4935. 10.1136/bmj.j4935 29367198

6 Smith AJ, Clutton RE, Lilley E, Hansen KEA, Brattelid T. PREPARE: guidelines for planning animal research and testing. *Lab Anim* 2018;52:135-41. 10.1177/0023677217724823 28771074

7 Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol* 2010;8:e1000412. 10.1371/journal.pbio.1000412 20613859

bmj.com/content/bmj/360/bmj.k760.full.pdf

bls.gov/ooh/images/3077.jpg

PREPARE

ARRIVE

dreamstime.com

Why do we need PREPARE when we have ARRIVE?

The ARRIVE guidelines claim that they 'provide a logical checklist with all the things that need to be considered when designing an experiment' *

In our experience when planning animal research, **a number of additional points need to be addressed at the planning stage**.

These items improve

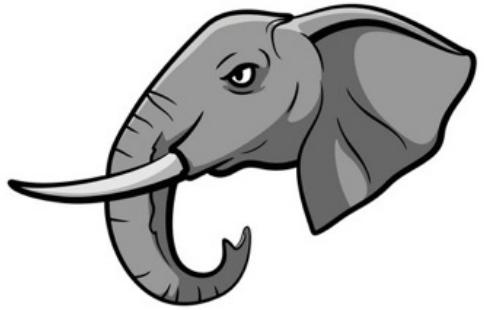
- ✓ **study quality and scientific validity**
- ✓ **animal welfare**
- ✓ **health and safety for both the animals and the humans affected directly or indirectly by the work**

*http://www.nc3rs.org.uk/sites/default/files/documents/Guidelines/ARRIVE%20Guidelines%20Speaker%20Notes.pdf

The elephants in the room…

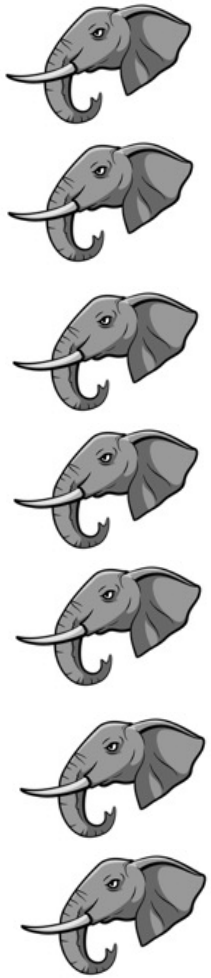
reddit.com

…the largest of them all is **inadequate attention to detail during planning** of animal studies,
including **collaboration with the animal facility from day one**



Some of the elephants...

- poor literature searches
- lack of humane endpoints
- poor study design, including choice of procedures
- vague distribution of work and costs between the scientists and the animal facility
- insufficient evaluation of the facility's competence and infrastructure
- too little attention to transport and acclimation
- ignoring health risks for all involved
- lack of standard procedures for necropsy
- poor planning of waste disposal
- little discussion about the fate of the animals



Check for updates

Original Article

PREPARE: guidelines for planning animal research and testing

Adrian J Smith[1], R Eddie Clutton[2], Elliot Lilley[3], Kristine E Aa Hansen[4] and Trond Brattelid[5]

Laboratory Animals
2018, Vol. 52(2) 135–141

DOI: 10.1177/0023677217724823
journals.sagepub.com/home/lan
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Abstract

There is widespread concern about the quality, reproducibility and translatability of studies involving research animals. Although there are a number of reporting guidelines available, there is very little overarching guidance on how to *plan* animal experiments, despite the fact that this is the logical place to start ensuring quality. In this paper we present the PREPARE guidelines: Planning Research and Experimental Procedures on Animals: Recommendations for Excellence. PREPARE covers the three broad areas which determine the quality of the preparation for animal studies: formulation, dialogue between scientists and the animal facility, and quality control of the various components in the study. Some topics overlap and the PREPARE checklist should be adapted to suit specific needs, for example in field research. Advice on use of the checklist is available on the Norecopa website, with links to guidelines for animal research and testing, at https://norecopa.no/PREPARE.

Keywords

guidelines, planning, design, animal experiments, animal research

Date received: 5 April 2017; accepted: 27 June 2017

Introduction

The quality of animal-based studies is under increasing scrutiny, for good scientific and ethical reasons. Studies of papers reporting animal experiments have revealed alarming deficiencies in the information provided,[1,2] even after the production and journal endorsement of reporting guidelines.[3] There is also widespread concern about the lack of reproducibility and translatability of laboratory animal research.[4–7] This can, for example, contribute towards the failure of drugs when they enter human trials.[8] These issues come in addition to other concerns, not unique to animal research, about publication bias, which tends to favour the reporting of positive results and can lead to the acceptance of claims as fact.[9] This has understandably sparked a demand for reduced waste when planning experiments involving animals.[10–12] Reporting guidelines alone cannot solve the problem of wasteful experimentation, but thorough planning will increase the likelihood of success and is an important step in the implementation of the 3Rs of Russell & Burch (replacement, reduction, refinement).[13] The importance of attention to detail at all stages is, in our experience, often underestimated by scientists. Even small practical details can cause omissions or artefacts that can ruin experiments which in all other respects have been well-designed, and generate health risks for all involved. There is therefore, in our opinion, an urgent need for detailed but overarching guidelines for researchers on how to plan animal experiments which are safe and scientifically sound, address animal

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[4]Section of Experimental Biomedicine, Department of Production Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Oslo, Norway
[5]Division for Research Management and External Funding, Western Norway University of Applied Sciences, Bergen, Norway

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UFAW

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PREPARE

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.

Two pages, available in 17 languages so far

The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

[1]The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK, [2]School of Veterinary Science, University of Bristol, Bristol, UK, [3]School of Biological Sciences, University of Bristol, Bristol, UK, [4]National Heart and Lung Institute, Imperial College London, UK, [5]Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

	ITEM	RECOMMENDATION	Section/ Paragraph
Title	1	Provide as accurate and concise a description of the content of the article as possible.	
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	
INTRODUCTION			
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.	
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.	
METHODS			
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.	
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.	
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).	
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.	

The ARRIVE guidelines. Originally published in *PLoS Biology*, June 2010[1]

PREPARE:

Planning **R**esearch and **E**xperimental **P**rocedures on **A**nimals: **R**ecommendations for **E**xcellence

PREPARE covers 15 topics:

Formulation of the study

1. Literature searches
2. Legal issues
3. Ethical issues, harm-benefit assessment and humane endpoints
4. Experimental design and statistical analysis

Dialogue between scientists and the animal facility

5. Objectives and timescale, funding and division of labour
6. Facility evaluation
7. Education and training
8. Health risks, waste disposal and decontamination

Methods

9. Test substances and procedures
10. Experimental animals
11. Quarantine and health monitoring
12. Housing and husbandry
13. Experimental procedures
14. Humane killing, release, reuse or rehoming
15. Necropsy

Items in pink are not highlighted in ARRIVE

In addition to the checklist, much more information is available on norecopa.no/PREPARE

Links to quality guidelines worldwide on e.g. blood sampling, injection volumes, housing and husbandry, analgesia, humane endpoints, experimental design

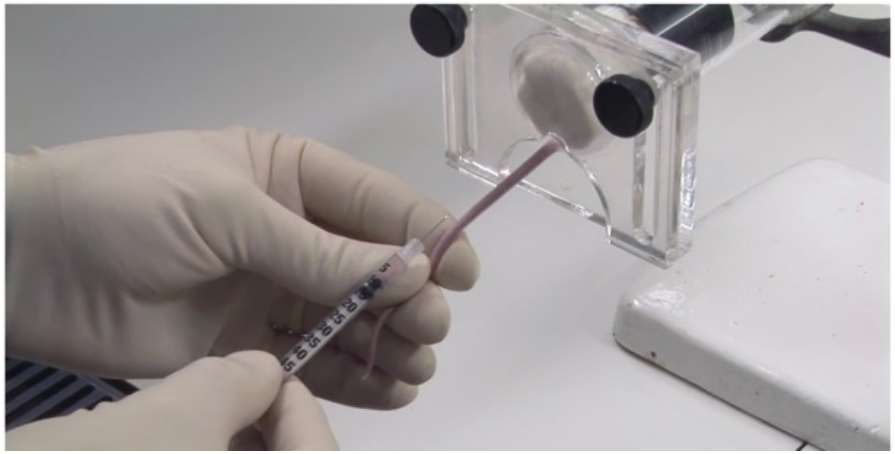
Contract between the animal facility and the research group

The division of labour and responsibilities between the two parties, with the aim of clarifying all stages of the experiment and ensuring that all necessary parameters are recorded.

https://norecopa.no/prepare/prepare-checklist

	Animal facility	Researcher	Not applicable
Animal:			
Arrival date			
Species			
Strain/stock and substrain			
Supplier (full name and address) or bred on the premises			
Number and sex			
Age, weight, stage of life cycle on arrival			
Pre-treatment (surgical or medical) from supplier			
Quality (e.g. SPF, germ-free, gnotobiotic, conventional)			
Acclimation time before the start of the experiment			
Time and duration of fasting (with/without water and bedding)			
Environment:			
Type of housing: barrier/conventional			
Temperature (mean ± variation)			
Light schedule			
Relative humidity (mean ± variation)			
Number of air changes in the animal room/cabinet per hour			
Environmental enrichment			
Housing:			
Free-range, shelf, cabinet, isolator			
Cage type and size			
Number and method of distribution of animals per cage			

An example: i.v. injection of a radioactive isotope:



procedureswithcare.org.uk/intravenous-injection-in-the-mouse

norecopa.no/PREPARE

PREPARE Checklist | 1-Literature searches | 2-Legal issues |
3-Ethical issues, Harm-Benefit Assessment and humane endpoints | 4-Experimental design and statistical analysis |
5-Objectives and timescale, funding and division of labour | 6-Facility evaluation | 7-Education and training |
8-Health risks, waste disposal and decontamination | 9-Test substances and procedures | 10-Experimental animals
11-Quarantine and health monitoring | 12-Housing and husbandry | 13-Experimental procedures |
14-Humane killing, release, re-use or re-homing | 15-Necropsy | Comparison with ARRIVE

https://www.wikivetlive.com/crisis-management-in-anaesthesia

Pilots use checklists, even on routine flights ...

Thanks to our main sponsors:

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- Laboratory Animals Ltd.
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- Norwegian Society for Protection of Animals (Dyrebeskyttelsen Norge)
- Novo Nordisk
- Scottish Accreditation Board
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- US Department of Agriculture, Animal Welfare Information Center (AWIC)

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