PREPARE before you ARRIVE: advice on how to plan animal studies from day one

norecopa.no/PREPARE

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

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Norecopa

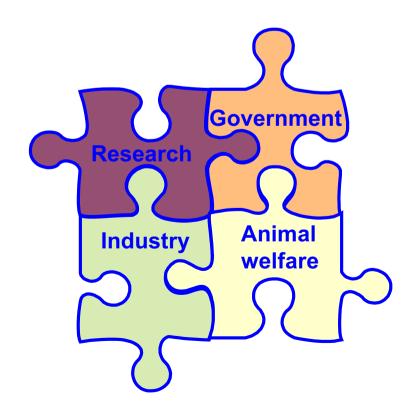
National Consensus Platform for the Replacement, Reduction and Refinement of Animal Experiments



ecopa.eu



- Established in 2000
- Recognises National Consensus Platforms (NCPs) with 4 stakeholders equally represented:



norecopa.no



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)

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U.S. Department of Agriculture

International consensus meetings

Harmonisation of the Care and Use of:

Fish (2005)

Wildlife (2008)

Fish (2009)

Agricultural animals (2012)

Wildlife 26-27 October 2017

All presentations and consensus statements are on the internet:

a lasting resource

International Meetings Calendar:





Original Article



PREPARE: guidelines for planning animal research and testing

Adrian J Smith¹, R Eddie Clutton², Elliot Lilley³, Kristine E Aa Hansen⁴ and Trond Brattelid⁵ Laboratory Animals
2018, Vol. 52(2): 135–141
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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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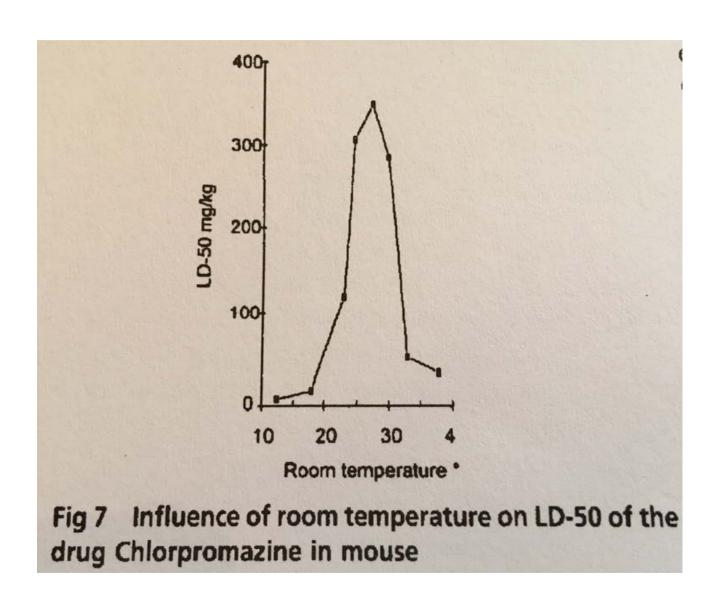
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Hurni 1969, quoted in Öbrink and Rehbinder

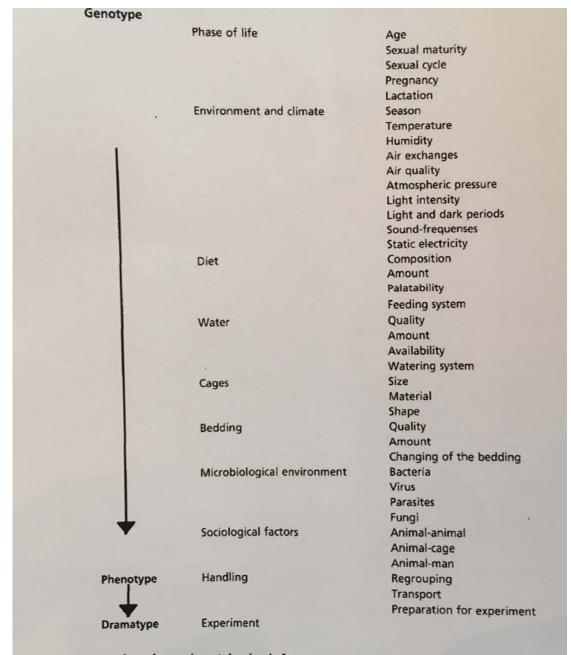


Fig 6 The generation of experimental animals from genotype over phenotype to dramatype

There are many guidelines for *reporting* animal studies

- GV-SOLAS committee, chaired by AW Ellery (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

More species- and situation- specific guidance is needed

Guidelines for reporting the results of experiments on fish

Trond Brattelid & Adrian J. Smith

Laboratory Animal Unit, The Norwegian School of Veterinary Science, PO Box 8146 Dep., 0033 Oslo, Norway

Summary

A detailed account of experimental design, including an accurate description of the animals used, is an essential part of good research practice. Without these details, the reader will be unable not only to form an opinion on the significance of the findings but also to repeat the experiment in another laboratory. This paper presents suggested guidelines for reporting experimental studies using fish.

Keywords Fish; experiment; study; report; refinement

Laboratory Animals, 2000

Published online on 9 May 2011 Lab Anim. doi: 10.1256/a.2011.010181

Working Party Report

Guidance on the severity classification of scientific procedures involving fish: report of a Working Group appointed by the Norwegian Consensus-Platform for the Replacement, Reduction and Refinement of animal experiments (Norecopa)

P Hawkins (Convenor)¹, N Dennison², G Goodman³, S Hetherington⁴, S Llywelyn-Jones⁵, K Ryder² and A J Smith⁸

*Research Animals Department, RSPCA, Witherforce Way, Southwater, West Suppos RHS SRS, UK *Animals (Scientific Procedures) Inspectionate, Home Office, PO Box 6779, Dundee DO1 9WW, UK; "Bological Services, The University of Edinburgh, Charcelor Building 49, Little France Crescent, Edinburgh EH16 45B, UK; "CEFRS, Palesfeld Road, Lowestoft, NRS Biological Services Unit, 4th floor, Hodglin Building, Guy's Campus, London SE1 TUL, UK, "Noracopa, c./o Norwegian Veterinary Institute, PO Box 750 Sentrum, N-0100 Oslo, Norway
Corresponding author: P Hawkins, Email: phawkinstitispos.org.uk

Abstract

The severity classification of procedures using animals is an important tool to help to cus the implementation of refinement an to assist in reporting the application of the 3Rs (replacement, reduction and refinement). The recently revised Directive that regulates animal research and testing within the European Union requires Member States to ensure that all procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe', using assignment criteria set out by the European Commission (EC). However, these are focused upon terrestrial species, so are of limited relevance to fish users. A Working Group set up by the Norwegian Consensus-Platform for the 3Rs (Norscopa) has produced guidance on the classification of severity in scientific procedures involving fish, including examples of "subthreshold", "midt", "moderate", "severe" and "upper threshold" procedures. The aims are to complement the EC guidelines and help to ensure that suffering in fish is effectively predicted and minimized. Norecopa has established a website (www.norecopa.no/categories) where more information on severity classification for procedures using fish, including field research, will be made available.

Laboratory Animals 2011: 1-6, DOI: 10.1258/la.2011.010181

Background

An effective prediction of the effects of a research protocol not a project should be licensed or funded. on the animals concerned helps to ensure that any pain, suf-faring or distress they may experience will be effectively articipated, recognized and allowing the secretal non-activative recognized and allowing the secretal non-activative recognized and allowing the secretal non-sured case of the secretal non-positive recognized and allowing the secretal non-ticipated recognized and allowing the secretary non-ticipa of severity are also fundamental to the harm-benefit and or severe on a case-by-case basis, using the assignment

assessments undertaken by bodies such as weulatory auth orities and ethical committees when deciding whether or

only for artists welfare but also for scientific visibility, because physiological and behavioural responses to suffering an significantly affect data and the second of t [seplacement, reduction and refinement) of Ransell and atton process and providing tools for monitoring compliance. Which is now an integral part of the legislation of animal research and tisting in many countries. Predictions procedures are classified as 'non-recovery,' rinid,' 'moder-procedures are classified as 'non-recovery,' rinid,' 'moder-procedures' recovery,' rinid,' 'moder

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P Hawkins, N Dennison, G Goodman, S Hetherington, S Llywelyn-Jones, K Ryder and AJ Smith

Laboratory Animals, 45: 219-224, 2011 norecopa.no/categories



Guidance on the severity classification of procedures involving fish

Report from a Working Group convened by Norecopa



Swiss survey highlights potential flaws in animal studies

Poor experimental design and statistical analysis could contribute to widespread problems in producing 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



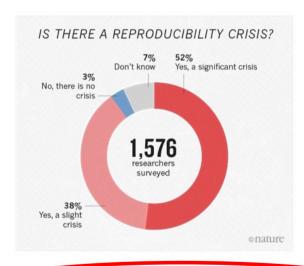
NATURE | NEWS FEATURE

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 read from Nature's survey of 1,576 researchers who took a brief online questionne reproducibility in research.

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 not only improve study quality and animal welfare (and therefore reproducibility), but also the safety of humans and animals affected directly or indirectly by the work.

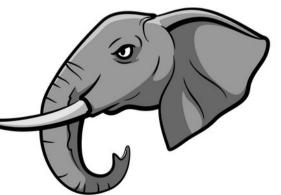
^{*}http://www.nc3rs.org.uk/sites/default/files/documents/Guidelines/ARRIVE%20Guidelines%20Speaker%20Notes.pdf

The elephants in the room...

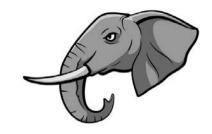


reddit.com

...the largest of them all is the lack of focus on planning animal experiments









ohiobirdsanctuary.com

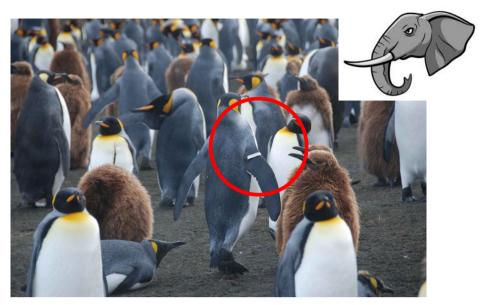
The stress of capture and restraint!

"Simple" identification methods?



Photo: T. Poppe, NMBU

Tags can collect seaweed and shellfish, which dramatically reduce the fish's ability to swim efficiently



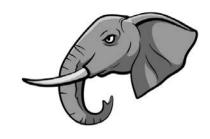
http://blogs.discovermagazine.com/notrocketscience/2011/01/12/flipperbands-impair-penguin-survival-and-breeding-success/#.VLU6_8Y7_wo

Flipper bands can reduce the penguin's ability to swim efficiently



Photo: colourbox.com

Many animals can be identified by non-invasive biometric methods, like photographing the pattern of stripes on the zebra





Contingent suffering

(not just direct suffering caused by the procedure) e.g. fear, boredom, discomfort

which may caused by

e.g. transport, housing, husbandry, social hierarchy

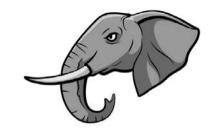
photo: NMBU

Single-housed male mice show symptoms of what in humans would be characterised as depression

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111065







News > Science

Scores of scientific studies based on mice thrown into doubt because they were picked up by the tail

Mice picked up by the tail – standard practice in labs – are stressed and anxious so don't act naturally in some experiments, new study finds

lan Johnston Science Correspondent | @montaukian | Tuesday 21 March 2017 10:58 GMT | 🖵 3 comments

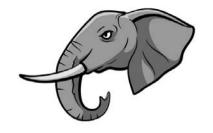
"Simple" techniques?



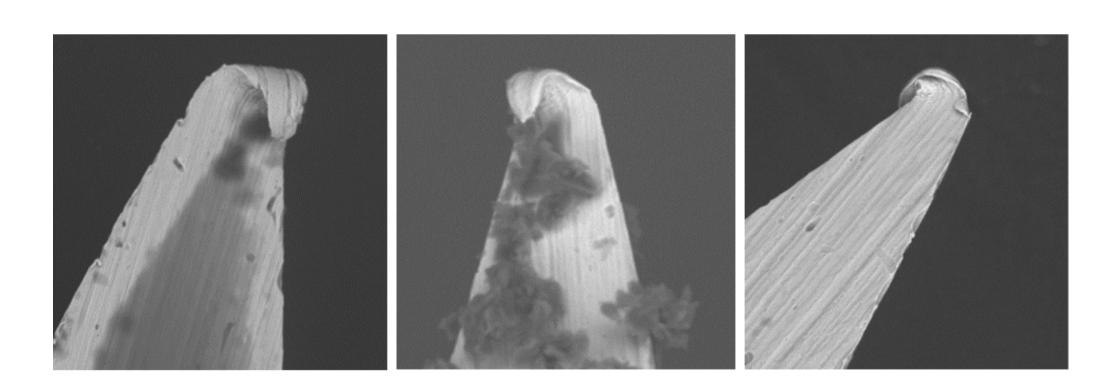


Photo: NMBU

- Are you sure that your injection ends up in the same place each time?
- Are the injections painful?
- Are they feasible? e.g. intramuscular injections in small animals



Disposable needles are designed to be used only once!



Lucy Whitfield, RVC and Sally Robinson, AstraZeneca Photo: AstraZeneca

https://www.nc3rs.org.uk/news/re-use-needles-indicator-culture-care

'the drug was administered by gavage in 3 daily doses'



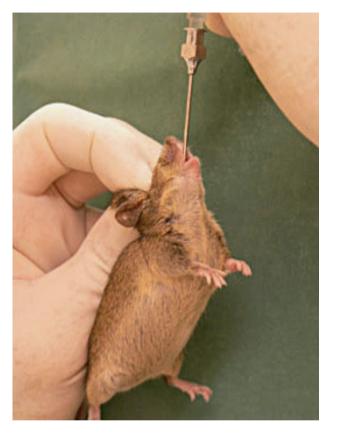


photo: NMBU

"How much ethanol do I need to give a mouse to be the equivalent of 2 glasses of red wine in the evening?"

Carefully consider the dose, use of allometric scaling, and the method of administration

'Simple' blood sampling techniques?

At the doctor:

I think I'll take a blood sample from you tomorrow.

I take my blood samples by sticking a knife into your neck, without anaesthesia.

But don't worry, I'll inject 2 litres of liquid into your abdomen first so you don't die from fluid loss.





medipoint.com/html/for_use_on_mice.html

The best blood sampling techniques are those where you can (1) see the blood vessel, (2) control the amount of blood you remove, (3) stop the bleeding easily and (4) not damage surrounding tissue.

Carol M. Newton (1925-2014)



National Library of Medicine

The three S's

- Good Science
- Good Sense
- Good Sensibilities

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.

https://norecopa.no/3S

The use of animals in education and training



frame.org.uk

'We may need the animals, as it were, on the night; but the machines will do very well at rehearsals'

norecopa.no/education-training/homemade-educational-materials











Workshop 11 April in Oslo

norecopa.no/education-training/homemade-educational-materials



https://www.bls.gov/ooh/images/3077.jpg

PREPARE

ARRIVE



https://www.dreamstime.com



Reporting guidelines like ARRIVE describe the experiment.
Guidelines like PREPARE are used to plan the experiment (choose the «ingredients» and «baking time»)

PREPARE:

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

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

PREPARE



The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Adrian J. Smith^o, R. Eddie Clutton^b, Elliot Lilley^c, Kristine E. Aa. Hansen^d & Trond Brattelid^o

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PREPARE! consists of planning guidelines which are complementary to reporting guidelines such as ARRWE².

PREPARE covers the three broad areas which determine the guality 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.					
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.					

Topic	Recommendation					
(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 preparati 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 pr 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.

- Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattellid T. PREPARE: Guide lines for Planning Animal Research and Testing. Labora tory Animals, 2017, DOI: 10.1177/0023677217724823.
- Kilkenny C, Browne WJ, Cuthill IC et al. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. PloS Biology, 2010; D0I: 10.1371/journal.pbio.1000412.

Further information

https://norecopa.no/PREPARE | post@norecopa.no | 🕥 @norecopa

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

In addition to the checklist, much more information is available on:

norecopa.no/PREPARE



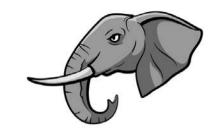
norecopa.no/PREPARE



Harm-Benefit Assessment

Harm-Benefit assessment, an evaluation of the likely sources and level of suffering of a planned procedure, followed by an assessment of the potential benefits of the research weighed against these harms, lies at the heart of legislation in the EU and elsewhere. A framework for severity assessment and severity classification must be established and justified. The likely adverse effects of each procedure should be described, along with their likely incidence and methods of recognising them, with indications of how these effects can be mitigated by implementing refinement. This necessitates the involvement of personnel with the relevant expertise to recognise, assess and reduce animal suffering, especially severe suffering. Guidance on this is available on the RSPCA website . Pecific justification of all unalievisted animal suffering must be provided. An estimate must be made of the maximum amount of pain, distress or lasting harm to which an individual can be exposed.

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



Health risks: there are many people to think about

People engaged in animal capture, transport and breeding

Animal carers and technologists

Security personnel

Administrative personnel with occasional access to the animal facility

Students

Sales representatives and those delivering supplies or equipment

Craftsmen carrying out facility repairs

Other visitors, including inspectors, journalists and students

Cleaning staff

Waste disposal personnel

Those who re-home research animals

Many of these people often possess a number of features which increase their health risks



They may:

- enter the facility outside normal working hours, when advice on hazards may not be readily available
- **not understand** messages left in the facility, especially if scientific jargon is used. Special consideration should be paid to employees with other native languages.
- have little knowledge of animal research, scientific method and the need for controlled experiments
- have no intrinsic concern of potential health hazards unless these are pointed out to them. Ironically, the cleaner and tidier an animal facility appears to be, the less likely they are to be fearful of such hazards.
- have not been health-screened before entering the facility. Those
 predisposed for allergy or asthma are particularly at risk when
 working with animals.
- be planning a family. Early embryonic development and spermatogenesis are known to be at risk upon exposure to ionising radiation and chemicals, including volatile anaesthetics.

Are we prepared for equipment failure?

Anything that can go wrong, will go wrong (Murphy's Law)

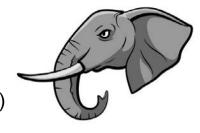
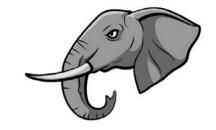




Photo: NMBU





norecopa.no/farm-animals

We strongly recommend the PREPARE checklist and its associated webpages with more detailed recommendations. Some, but by no means all, of the challenges include:

- > health status, acquisition, transport and acclimation to new buildings
- > quarantine and adaptation to new feeding regimes
- > establishment of new social groups
- > provision of sufficient space for exercise, sampling, anaesthesia and necropsy
- > ventilation issues
- > the differences in practices between traditional farm work and those used in controlled studies in a laboratory environment
- > health, safety and general hygiene
- > waste disposal (e.g. contaminated carcases)
- > containment of pathogens
- > identification of sufficient numbers of staff who are familiar with, and competent to handle, farm animal species

Many of these issues are exacerbated by the sheer size of the animals.

Contract between the animal facility and the research group

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

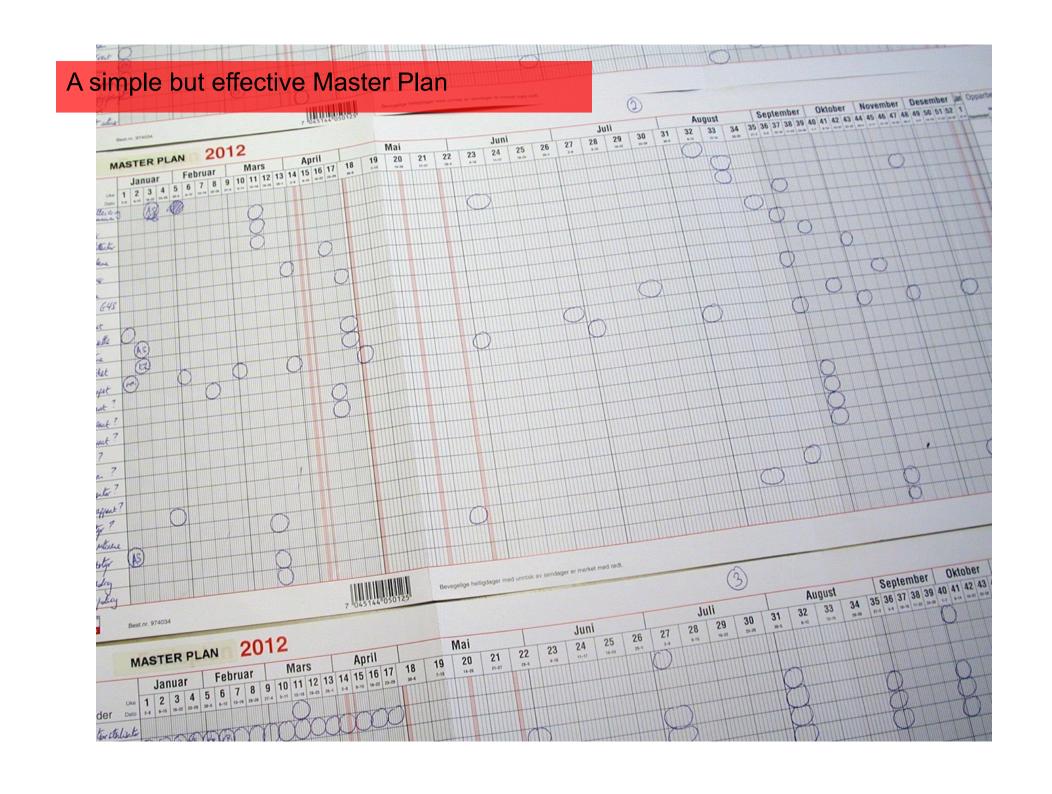


	Animal	Researcher	Not		
	facility		applicable		
Animal:					
Arrival date					
Species					
Strain/stock and substrain					
Supplier (full name and address) or bred on the premises					
Number and sex					
Age, weight, stage of life cycle on arrival					
Pre-treatment (surgical or medical) from supplier					
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					

Quality assurance and a culture of care at all levels of the animal facility

- SOPs describing good techniques, carried out by competent operators
- Checklist ("contract") between researcher and the facility
- The AAALAC Program Description template* as an overall performance checklist
 - Institutional policies on animal care and use
 - Animal environment, housing and management
 - Veterinary care
 - Physical plant
- A Master Plan as a weekly checklist for the whole facility during the year

^{*}https://www.aaalac.org/programdesc/index.cfm



Think "3R-Alternatives" at all stages

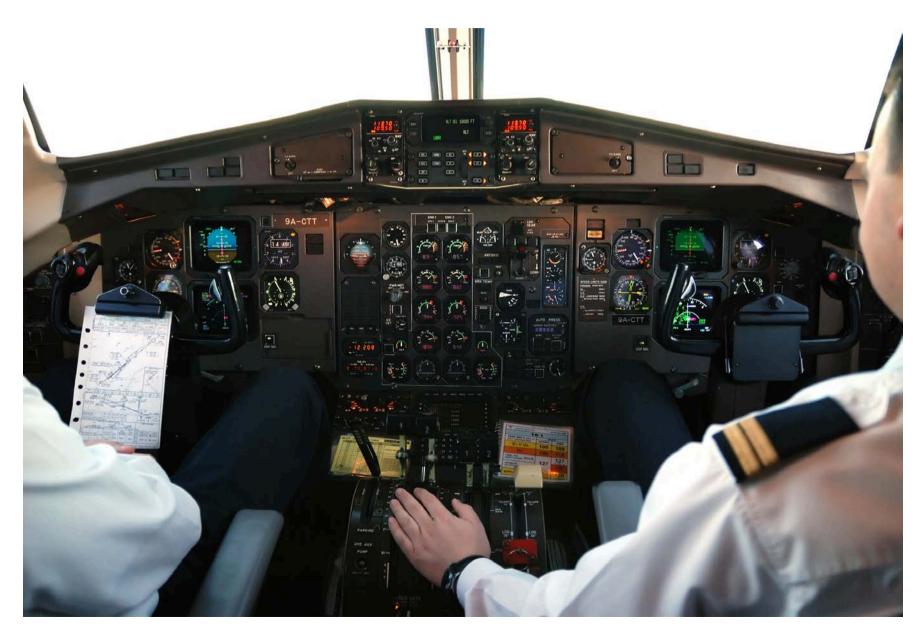
- Breeding
- Transport
- Acclimation
- Procedures, e.g. choice of
 - dose
 - method of administration
 - methods of data collection (blood sampling, body temperature, heart rate, blood pressure etc.)
- Pilot studies

Consult the technicians from Day 1:

- they have a right to know and will be more motivated
- they know the possibilities (and limitations) in the animal facility
- they often possess a large range of practical skills and are good at lateral thinking
- they know the animals best
- the animals know them best

Even experienced pilots use checklists as an aide memoire...







wikipedia.org

Søren Kirkegaard (1813-1855)

It is perfectly true, as philosophers say, that life must be understood backwards. Reporting!

But they forget the other proposition, that it must be lived forwards. PREPARE!



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Graphics: colourbox.com

















