Are we Car Salesmen, Boy Scouts or Airline Pilots? Preparing for robust and humane research

norecopa.no/WC11-PREPARE

Adrian Smith adrian.smith@norecopa.no



https://norecopa.no



The evolution of the PREPARE planning guidelines:



- Discussions and learning material on courses in Laboratory Animal Science from 1986 onwards
- Development of planning guidelines too obvious to publish!
- 15 minutes to present 30 years of work...
- Ine realisation that the community was asking for planning guidelines, not just reporting guidelines
- Published ahead of print in August 2017

norecopa.no/legislation/eu-directive-201063

Norecopa: PREPARE for better research

Norecopa

Norway's National Consensus Platform for the

Three Rs: Replacement, Reduction and Refinement

and a source of global 3R resources

https://norecopa.no



norecopa.no: an updated overview of global 3R resources



Design and reporting of animal experiments

This page supplements advice given in <u>Section 4 of the PREPARE guidelines</u>. PREPARE covers all aspects of design (including animal and facility related issues).







Sales, Profit

Us: citations, impact factor, publication list





Integrity, Preparedness

Us: Research integrity, validity, reproducibility



Collaboration, Precision, Reliability, Safety

Us: the same!



PREPARE is all about quality assurance...





'Our long experience and modern coffee machines are your guarantee of quality'??

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Two frustrations

"We can solve the reproducibility crisis by

- courses in "Experimental Design" that focus primarily on the "mathematical" aspects (e.g. randomisation, experimental units, blinding, statistical methods)
- better reporting"







Reporting guidelines are not new... e.g.

- Guidelines for specification of animals and husbandry methods when reporting the results of animal experiments, **1985** (GV-SOLAS)
- Reporting animal use in scientific papers, 1997 (Smith et al.)
- Animal definition: a necessity for the validity of animal experiments? 2000 (Öbrink & Rehbinder)
- Guidelines for reporting the results of experiments on fish, 2000 (Smith & Brattelid)
- ARRIVE Guidelines, 2010 (Kilkenny et al.)
- Gold Standard Publication Checklist (GSPC), 2010 (SYRCLE)
- Institute for Laboratory Animal Research, 2011 (NRC)
- Instructions to authors, in many journals
- ARRIVE 2.0 Guidelines, 2019 (Percie du Sert et al.)





Reporting

Planning

nature human behaviour



Perspective | Open Access | Published: 10 January 2017

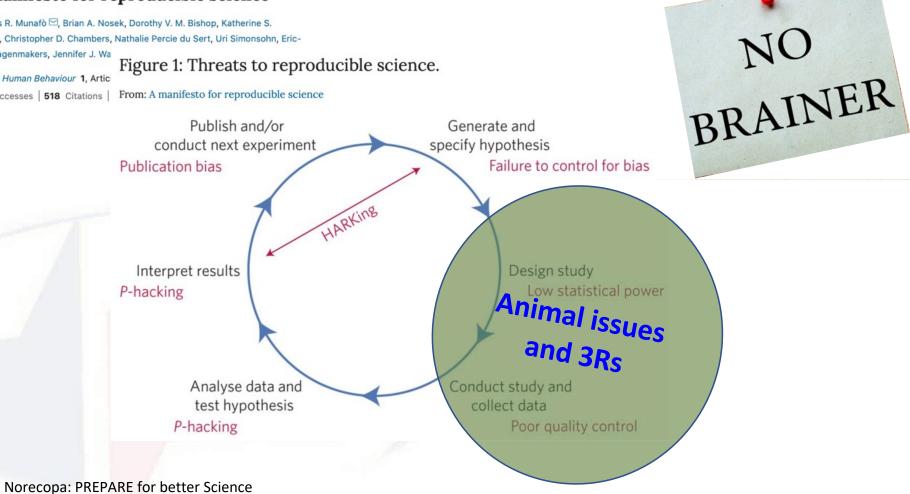
A manifesto for reproducible science

Marcus R. Munafò ⊡, Brian A. Nosek, Dorothy V. M. Bishop, Katherine S. Button, Christopher D. Chambers, Nathalie Percie du Sert, Uri Simonsohn, Eric-Jan Wagenmakers, Jennifer J. Wa

Figure 1: Threats to reproducible science.

Nature Human Behaviour 1, Artic

33k Accesses | 518 Citations | From: A manifesto for reproducible science



1994:

Neglected Factors in Pharmacology and Neuroscience Research: Biopharmaceutics, Animal Characteristics, Maintenance, Testing Conditions

By Claassen, Volkert

Record number: 13335 (legacy id: 6153)

The objective of this book $\underline{\mathbb{C}}^{\bullet}$ is to indicate those variables which in general may need a better control. Examples, gathered from the literature, are presented to illustrate the impact that those neglected variables may have on various characteristics. The book presents a series of representatives studies from a broad field of interest so that insight can be obtained about the potential effects of these parameters in experimental outcomes. In this way, an impetus should be given to the critical consideration of test design and limitations of conclusions from experimental results. In part, the book is written as a reaction to frustrations endured during pharmacological research of many years' standing, and therefore the choice of examples from the literature is largely related to this discipline. As pharmacological research is to a large extent based on the other life sciences, this volume may



be the case for pharmacokineticists and toxicologists for whom drugs are the main object of study. This book may also help to improve test designs for biochemists and physiologists, not only when using drugs as tools in their experiments, but also to improve generally the control of animal characteristics and test conditions. This book is Volume 12 in a series entitled Techniques in the Behavioral and Neural Sciences.

Comments & References: First Edition. 496 pages. Paperback. A review is available in Laboratory Animals 7, April 1996, Volume 30 (2).

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Review:

'This book is essential reading for anybody that wishes to take the problem of experimental variability seriously. There are no magic cures offered for experimental problems, but there are many explanations offered within this book. A worthwhile addition to any library.'

norecopa.no/textbase/neglected-factors-in-pharmacology-andneuroscience-research-biopharmaceutics-animal-characteristicsmaintenance-testing-conditions









How do others achieve reproducibility?



https://www.meonuk.com/runway-markings-explained





10-15 checklists even on short routine flights





Checklists

- Reduce risk of forgetting to carry out vital actions
- Ensure checks are carried out in the correct sequence
- Encourage cooperation and cross-checking between crew members
- Make sure that everyone is "on the same page"

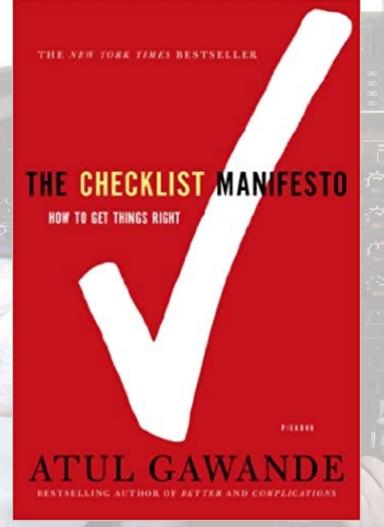
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Too late to read the checklists when you have ARRIVEd!



colourbox.com





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Surgical Safety Checklist



Patient Safety

A World Alliance for Safer Health Care

(with at least nurse and anaesthetist)	(with nurse, anaesthetist and surgeon)	(with nurse, anaesthetist and surgeon)
Has the patient confirmed his/her identity, site, procedure, and consent?	Confirm all team members have introduced themselves by name and role.	Nurse Verbally Confirms: The name of the procedure
Yes	Confirm the patient's name, procedure, and where the incision will be made.	Completion of instrument, sponge and nee
	Has antibiotic prophylaxis been given within the last 60 minutes?	Specimen labelling (read specimen labels a including patient name) Whether there are any equipment problem
	Yes Not applicable	addressed
□ Yes	Anticipated Critical Events	To Surgeon, Anaesthetist and Nurse: ☐ What are the key concerns for recovery an
Is the pulse oximeter on the patient and functioning? Yes	To Surgeon: What are the critical or non-routine steps? How long will the case take?	management of this patient?
Does the patient have a:	☐ What is the anticipated blood loss?	
Known allergy?	To Anaesthetist:	
□ No	☐ Are there any patient-specific concerns?	
☐ Yes Difficult airway or aspiration risk? ☐ No ☐ Yes, and equipment/assistance available Risk of >500ml blood loss (7ml/kg in children)? ☐ No ☐ Yes, and two IVs/central access and fluids	To Nursing Team: Has sterility (including indicator results) been confirmed? Are there equipment issues or any concerns?	
	Is essential imaging displayed? Yes Not applicable	
planned		

who.int/patientsafety/topics/safe-surgery/checklist/en

amazon.com/gp/product/0312430000





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

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.

guidelines, planning, design, animal experiments, animal research

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

Introduction

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 lines for researchers on how to plan animal experiments 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 arte-The quality of animal-based studies is under increasing facts 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 guidewhich are safe and scientifically sound, address animal

> Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750. Sentrum, Oslo, Norway

Midlothian, UK ³Research Animals Department, Science Group, RSPCA, Southwater, Horsham, West Sussex, UK Section of Experimental Biomedicine, Department of Production

Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Oslo, Norway Division for Research Management and External Funding Western Norway University of Applied Sciences, Bergen, Norwa

Adrian Smith, Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750 Sentrum, 0106 Oslo, Norway. Email: adrian.smith@norecopa.no

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All those who contributed to the development of PREPARE, and in particular the co-authors:

Eddie Clutton, Elliot Lilley, Kristine Hansen & Trond Brattelid

the responsibility for this presentation is mine alone

Pre-published under Open Access on 3 August 2017, sponsored by the Universities Federation for Animal Welfare (UFAW), UK

https://doi.org/10.1177/0023677217724823



Over 19,000 downloads from the journal website so far



PREPARE:

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

PREPARE covers 15 topics:

Formulation of the study

- 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

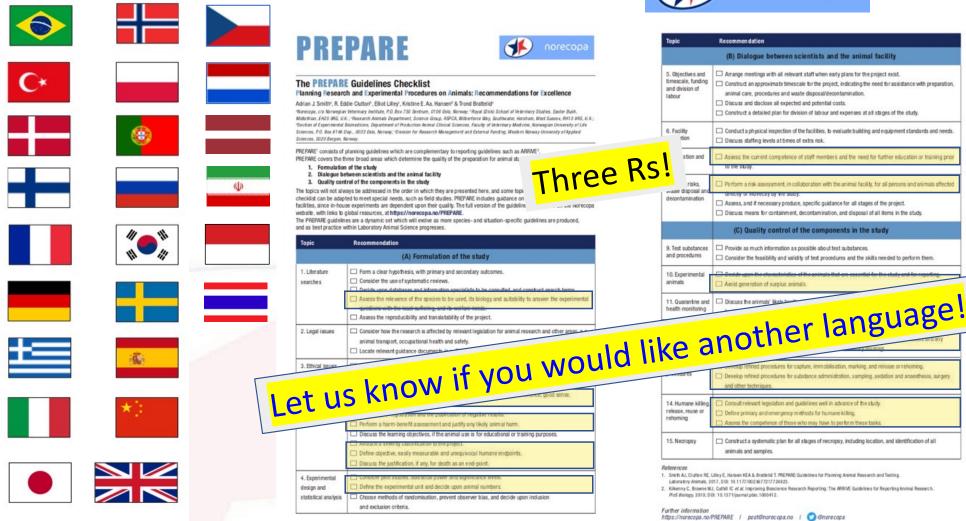
- 9. Test substances and procedures
- 10. Experimental animals
- 11. Quarantine and health monitoring
- 12. Housing and husbandry
- 13. Experimental procedures
- 14. Humane killing, release, reuse or rehoming
- 15. Necropsy

Maybe the study should not go ahead

Systematic review of published research?

norecopa.no/PREPARE/prepare-checklist







PREPARE:

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Methods

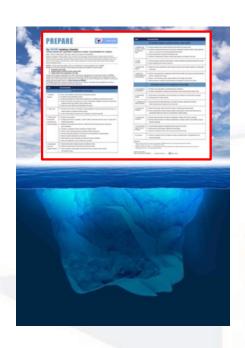
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- 12 Housing and husbandry
- 13. Experimental procedures
- 14 Humane killing, release, reuse or rehoming
- 15 Necropsy

Items in pink are not typically highlighted in reporting guidelines



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

norecopa.no/PREPARE







PREPARE PREPARE checklist Comparison with ARRIVE Endorsements Film 1-Literature searches 2-Legal issues 3-Ethical issues,

PREPARE

The PREPARE Guidelines, and this section of the Norecopa website, have been developed with the involvement and support of the RSPCA &.

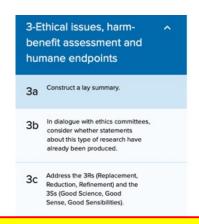


As part of ongoing efforts to reduce waste, promote animal alternatives (all the three Rs), and increase the reproducibility of research and testing, a group of experts from the UK and Norway, led by Norecopa, has produced a set of guidelines for planning experiments:

PREPARE (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence)

norecopa.no/PREPARE





- 5. Have the experiments been carried out before, and is any repetition justifiable?
- 6. What approaches to reduce distress r have been considered?



 Have national or local research ethics committees already produced statements relevant to the research being planned? Consideration should also be paid to the broader context of the research. For example, research directed at increasing the productivity of farming at the expense of (or without improving) individual animal welfare, or wildlife research whose primary aim is population management.

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

nd will any advances in this ses only index the title and rejected?

Assessment and justily any likely animal harm.

3f Discuss the learning objectives, if the animal use is for educational or training purposes.

3g Allocate a severity classification to the project.

3h Define objective, easily measurable and unequivocal humane endpoints.

3i Discuss the justification, if any, for death as an end-point.

and statistical analysis

- 3. Have the Three S's (Good Science, Good Sense and Good Sensibilities 2) been addressed? Sufficient time should be allocated to this point, since two of the three S's are highly subjective, but equally important. The use of commonsense and critical anthropomorphism are justifiably part of the work to assess the impact of research on animals, not least when a scientific evidence base does not exist.
- 4. Does the proposed study have a clear rationale and scientific relevance, and what will be the next step if the hypothesis is supported or rejected?
- 5. Have the experiments been carried out before and is any repetition justifiable?
- 6. What approaches to reduce distress rehave been considered?
- 7. Will the preject undergo pre-registration of and will regative results be published, to avoid publication bias?

Many more links to resources on ethics are available here ♂.

Details also ut pre-registration of animal studies and reporting of critical incidents are to be found in the section on Experimental Design and Statistical Analysis C^* .

Harm-Benefit Assessment







The division of labour and responsibilities

Clarifying all stages of the experiment

Ensuring that all necessary data 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:		1	
Free-range, shelf, cabinet, isolator			
Cage type and size			
Number and method of distribution of animals per cage			





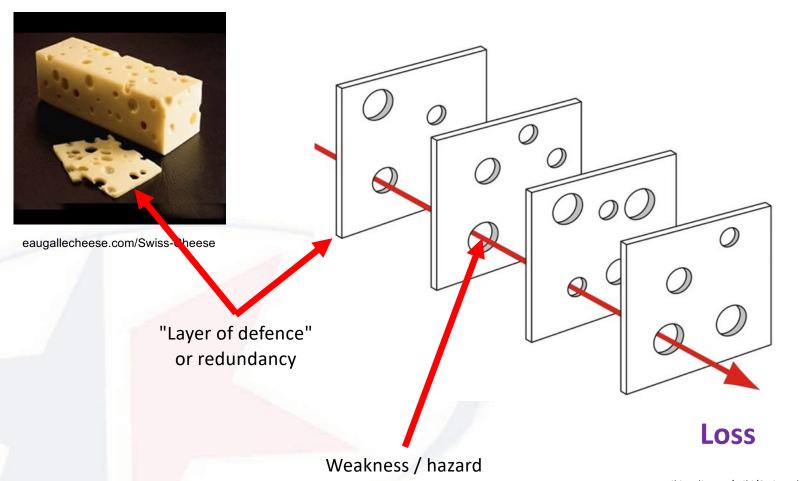
Program Description

- A. Animal Care and Use Program
- B. Animal environment, Housing and Managemen
- C. Veterinary Care
- D. Physical plant

III. Veterinary Care	
III. Veterinary Care A. Animal Procurement and Transportation	
A. Animal Procurement and Transportation 1. Animal Procurement	29
Animal Procurement Transportation of Animals B. Preventive Medicine	29
Transportation of Animals B. Preventive Medicine 1. Animal Biosecurity	29
1. Animal Biosecurity	29
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3. Separation by Health Status and Species C. Clinical Care and Management 1. Surveillance Diagnosis	30
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4. Diagnostic Resources 5. Drug Storage and Control D. Surgery 1. Pre-Surgical Planning 2. Surgical Facilities	32
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2. Surgical Facilities	32
3. Surgical Procedures 4. Aseptic Technique 5. Intraoperative Monitoring	32
4. Aseptic Technique	33
Aseptic Technique Intraoperative Monitoring	33
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Threat and Error Management



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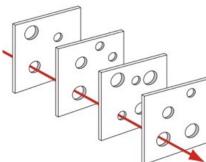
wikipedia.org/wiki/Swiss_cheese_model



A Contingency Plan, based upon risk assessment

- Access to emergency services (police, fire, medical and veterinary help, security guards, personnel transport in cases of acute illness)
- Means of communication with staff members at all levels
- SOPs for acute illness, including

to be revised or supplemented in the light of Covid-19



Temporary staff at weekends and holidays

These need

- bites
- corrosive injuries

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- and forms for reporting such injuries
- Firefighting, evacuation of personnel and animals
- Access to specialist services (e.g. ventilation system, plumbing, electrical installations, suppliers of equipment)
- Routines in cases of power failure, water leaks and (if applicable) natural disasters such as flooding
- Routines for emergency killing of animals
- Routines in cases of threats to the facility or personnel

https://norecopa.no/prepare/6-facility-evaluation/master-plan-and-sops/contingency-plan



Good advice is emerging from the Covid-19 pandemic

Suggested considerations for establishment working under ASPA during the COVID19 lock-down

CATEGORY			CONS	SIDERATIONS/SUGGESTIONS
PERSONNEL Provide 'essential worker' letter to show authorities, include home address. Consider whether company/ photo i.d. would be helpful All personnel must prioritise their health and the health of others by wearing suitable PPE and by observing social distancing as advised by the government	ANIMAL TECHNICIANS	team. Examples of how onsit shift / a late shift to reduce or responsibilities they may (if w Where teams can't be separa avoiding people not in PPE. P Review teams regularly – this Introduce regular and freque door plates, taps and work so	ble to lower the rise teams might be rontact and total st well enough) be absted use full PPE/ Fylysically segregates may need to be don't routines for sururfaces. Clean with	sk of transmission(each team is treated as 'household') to the wider run include alternate days, 2days on 2days off and utilising an early aff in an area at any one time. If people are in isolation or have caring let to work offsite as part of a "virtual office" team RPE and have staggered entry/break/exit times or other means of e in unit if possible laily in some situations face decontamination, paying particular attention to door handle/ in detergent / 70% isopropyl alcohol or similar commendate parking where accelled to allow individuals to traval by one. Ensure all alarm systems are checked regularly and are functional. Monitor, record and act on all alarms. Review contingencies for critical system failure (e.g. HVAC) and have an action plan. Make sure all backup systems are fully functional and that sufficient spare parts are available and accessible.
Support mental health Consider mindfulness apps,		ANIMALIS	VETS	norecopa.no/be-prepared equired
Convert empty animal room		ANIMALS	BREEDING	Ensure all non-replaceable lines are cryopreserved
nto a relaxation/yoga room	RESEARCHERS			Consider stopping breeding of lines that are frozen down and have been on "tick over"
(online yoga classes).				Breed only for colony management, i.e. minimum number of breeding pairs to maintain the health of the colony Avoid breeding animals with phenotype – maintain animals where homozygotes may be phenotypic as wild type in heterozygote crosses to avoid generation of homozygotes
				Genotype promptly in order to identify animals required for ongoing breeding and cull animals not required ASAP Consider outsourcing genotyping if internal facilities are closed
			REDUCE STOCK	Do not start new work unless absolutely essential/ internal review has been performed that confirms that the work can be properly serviced
				Essential research work may continue if staffing levels allow it. A local decision making process which records decision making as to which projects may remain ongoing should be in place. Examples of what may be reasonable are COVID-19 work, aged animal work and work to complete studies
	COTA DI IGUA CO			There may be reasons for prioritising ongoing work with some species (e.g. NHPs)
	ESTABLISHMENT			If the facilities allow, consolidate animals to one area, check light cycle, room temps & designation first
	LICENCE			Spread work evenly / reduce cleaning of cages – but not to extent that welfare could be compromised
	HOLDER			Re-assess stock levels /staff levels at least once per week
ENGINEERS	ENGINEERS			Cull animals that are not going to be needed for colony management and cannot otherwise be used Avoid unnecessary movement of animals
				Prioritise the movement of animals to other facilities or establishments for contingency of valuable lines.
		ACCESS		Check your facility/ies will be open – Provide a list of names requiring access. Check with security how and when essential staff will access
		411221124		Confirm how essential supplies and waste contractors will service the facility/ies
		SUPPLIES		Stock up on diet, bedding, nesting materials, PPE, disinfectants and other essentials, aim for a minimum of 3 mon
				Ensure there will there be Liquid nitrogen / dry ice for cryopreserved stocks
			1	Have stocks of CO₂ and sodium pentobarbitone and any other drugs as directed by the NVS
		ESTATES / ENGINEERS		Check your contractors are working and get emergency contacts. Maintain a list of mobile numbers, available to everyone
				Consider if essential equipment will require servicing or repair. Ensure that you have a plan to enable this
				Will waste be being removed from site? – prepare an area for on-site storage if necessary
		RECORDS		Record all difficult decisions taken. What/ when /why and any related evidence

lava.uk.net/viewtopic.php?f=3&p=80



Contingency and redundancy

Anything that can go wrong, will go wrong (Murphy's Law) when it's least convenient (Sod's Law)

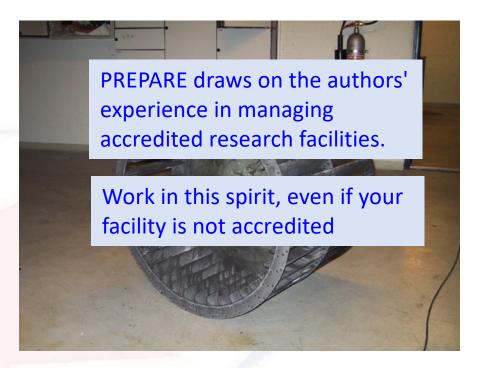


Photo: NMBU



CIRS-LAS Portal

Critical incident reporting system in laboratory animal science

Refine - Reduce - Replace



What if things go wrong?

MUTUAL LEARNING from errors, near misses, critical or even adverse events occurring in the context of animal experimentation prevents unnecessary repetition of unsuccessful experiments

CRITICAL DISCUSSIONS on causes and approaches to solutions lead to an increase in animal welfare

OPEN DIALOGUE ensures transparency in laboratory animal science

vimeo.com/358069203 or norecopa.no/PREPARE/film 3-minute cartoon film





Our hopes for PREPARE

- Uptake on a voluntary basis
- Interest from
 - funders
 - animal care & use committees
 - regulators
 - institutions
 - animal facilities
- Early career scientists
- Principal investigators

Endorsement doesn't necessarily mean compliance...

norecopa.no/PREPARE/endorsements



"We ARRIVED, because we were PREPARED"

- ✓ Better Science
- ✓ Improved animal welfare
- ✓ Advancement of the 3Rs
- ✓ Safer working environment

NO BRAINER

Thanks to Norecopa's main sponsors:



- Standing Committee on Business Affairs, Norwegian Parliament
- Norwegian Ministries of Agriculture and Fisheries
- Research Council of Norway
- Laboratory Animals Ltd.
- Architect Finn Rahn's Legacy
- Nordic Society Against Painful Experiments (NSMSD)
- Norwegian Society for Animal Protection (Dyrebeskyttelsen Norge)
- Norwegian Animal Protection Alliance (Dyrevernalliansen)
- Novo Nordisk
- Sanofi
- Scottish Accreditation Board (SAB)
- Stiansen Foundation
- Universities Federation for Animal Welfare (UFAW)
- US Department of Agriculture (USDA)

Graphics: colourbox.com



























(Monday 23 August Session S200, 3.30-5.30 p.m.)
Norecopa norecopa.no/WC11

Friday 27 August Session S113, 3.00-5.00 p.m. Wildlife research norecopa.no/WC11-wildlife

Tuesday 31 August Session S301, 6.30-8.30 p.m.

The Refinement Wiki norecopa.no/WC11-wiki



