Improving nonclinical research practices: way forward

2022. LAS webinar series organized by CroLASA in collaboration with SLAS

How can NORECOPA help researchers PREPARE for better science?

Adrian Smith, Norecopa

adrian.smith@norecopa.no

16 February 2022

norecopa.no/160222

"better science?"

- valid data (a true treatment effect)
- reproducible and translatable experiments
- best possible animal welfare
- health & safety (of animals and people)
- a culture of care in the research group
- communication of best practice to others

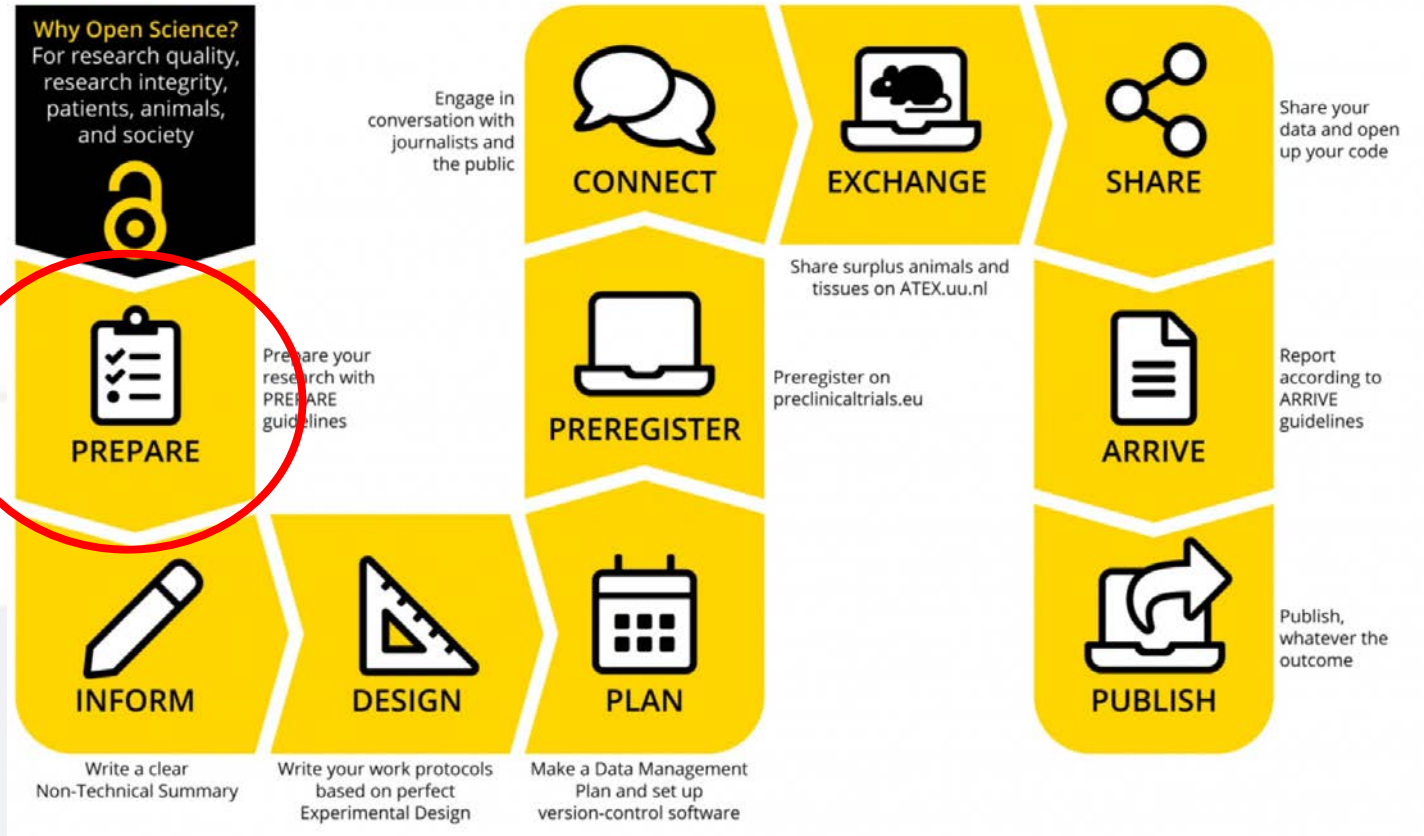
journal.eahn.org/article/id/7475

From the Master Builder...

...to a coordinated effort from many experts

Site work (excavation, waste & water, paths)
Metal structures
Concrete structures
Masonry
Carpentry (rough & visible)
Waterproofing and insulation
Escalators and lifts
Heating, ventilation and air conditioning
Plumbing
Electrical systems
Doors & windows
Fire protection
Painting
Landscaping
Rodent control

The path to better research



Norecopa: PREPARE for better Science

norecopa.no/PREPARE *and*
ivd-utrecht.nl/en/news/better-animal-research-through-open-science-1

Norway's National Consensus Platform for the

Three Rs: Replacement, Reduction and Refinement

and a source of *global* 3R resources

we welcome more from you!

https://norecopa.no

Established in 2007

Norecopa: PREPARE for better Science

EU3Rnet

norecopa.no/global3r

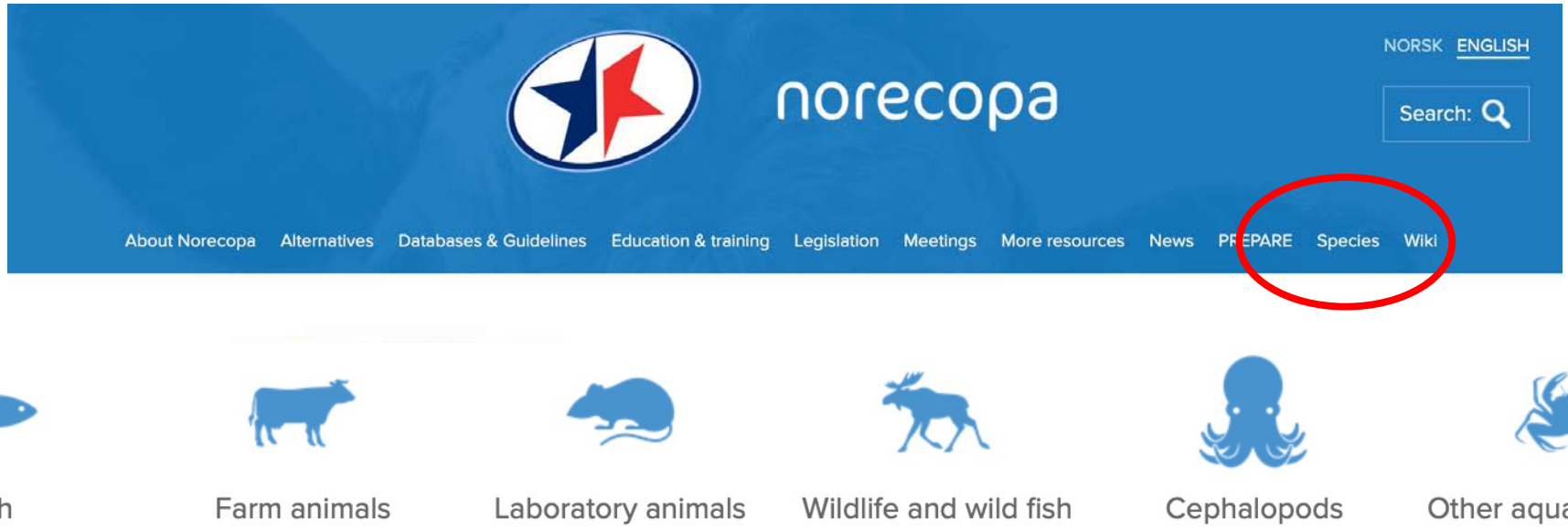
Norecopa: PREPARE for better Science

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

approx. 8,900 webpages
320,000 hits annually

7-8 detailed newsletters per year

Norecopa: PREPARE for better Science



Norecopa: PREPARE for better Science

+ webpages for past meetings and recorded meetings

norecopa.no/meetings/meetings-calendar

Webinar and Meetings calendar

January 2022

- Guide to improving reproducibility by networking, webinar (Marcus Munafo), 19 January 2022
- Traumeforsøg og "den gode ansøgning", miniseminar, 19 January 2022
- Refining mouse handling using tunnels or cupped hands: Why and How, NA3RsC webinar, 19 January 2022
- The Effects of Environmental Temperatures on Energy Expenditure in Mice, webinar (Marc Reitman & Oksana Gavrilova), 20 January 2022
- Evidence for pain in fishes: Implications for welfare, webinar (Lynne Sneddon), 25 January 2022
- FRAME Training School in Experimental Design, online, 25-28 January 2022 (draft programme)
- How the pharmaceutical industry is tackling 'severe' suffering in animals used in science, RSPCA/EFPIA webinar, 26 January 2022
- 2nd Next Generation Organ-on-Chip and Organoids workshop, Geneva, 26-27 January 2022
- ZEBREFINE - refinement opportunities for zebrafish anaesthesia, online meeting, 27 January 2022
- Injection or infusion? Insights for your next animal dosing investigation, Charles River webinar, 27 January 2022
- Demonstration of the Experimental Design Assistant (EDA), webinar, 27 January 2022
- Statistical Analysis for In Vivo and In Vitro Scientists course, 31 January - 2 February 2022

Pdf files of 80+ presentations held at Norecopa's meetings

Norecopa: PREPARE for better Science

Databases & Guidelines

Published lists of resources are difficult to search and quickly become outdated. Lists on a website are easier to search, but do not enable the use of filters or intelligent search engines.
Norecopa has therefore constructed four databases, which together with all the text on this website can be searched simultaneously using the search field at the top of every page.

- 3R Guide: a global overview of **databases, guidelines, information centres, journals, email lists, regulations and policies** which may be of use when planning experiments which might include animals. A quick overview of all the guidelines can be accessed here. Norecopa has written several of these, including the PREPARE guidelines for planning animal research and testing.
- NORINA: a global overview of audiovisual aids and other items which may be used as **alternatives or supplements to animals in education and training** at all levels from junior school to University, including dissection alternatives and surgical simulators.
- TextBase: a global overview of **textbooks and other literature within laboratory animal science** and related topics.
- Classic AVs: a subset of NORINA covering **audiovisual aids that are based on older technology**.

These databases are updated regularly. Please give us feedback if you discover errors or omissions.

The Norecopa website also includes four other collections:

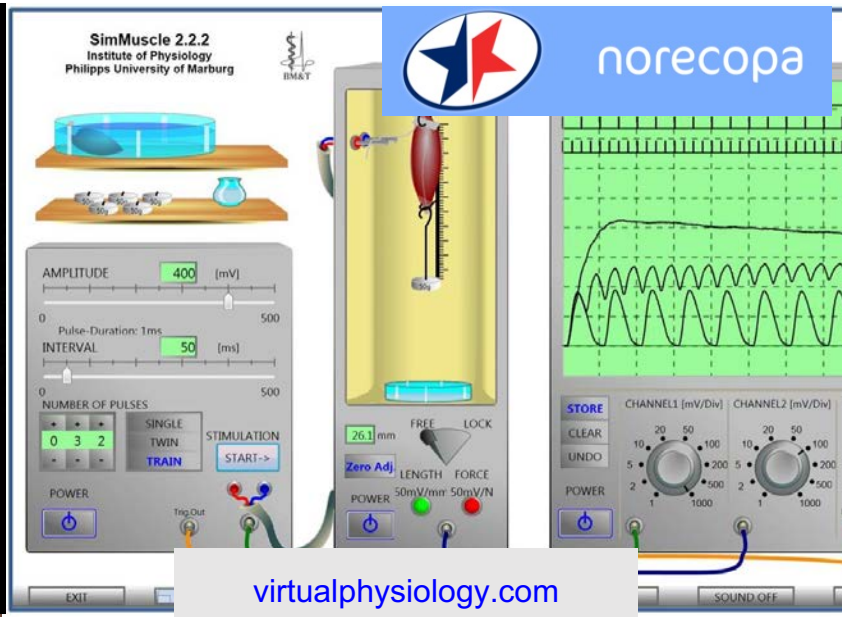
- NAL: a collection of literature references relating to the 3Rs from the US National Agricultural Library
- European Commission datasets:
  - 3Rs Knowledge Sources: over 800 resources collected by the Commission in 2016
  - 3Rs Education and Training Resources, over 560 items collected in 2018
  - Non-animal models for respiratory tract diseases, over 280 models identified in a literature review of over 21,000 publications

Here is an alphabetical global list of all the databases cited on the Norecopa website.

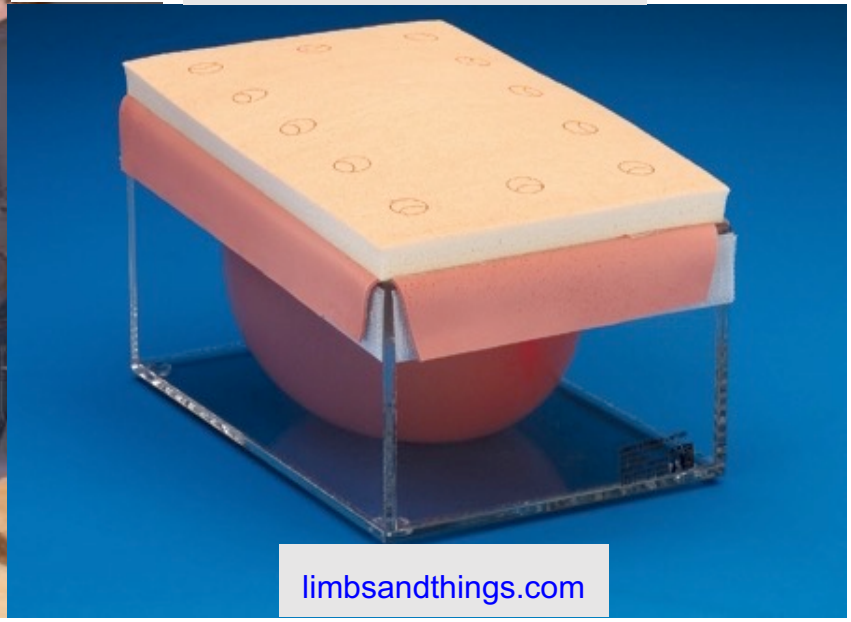
norecopa.no/databases-guidelines

links to over 70 other databases


norecopa.no/NORINA
3dglasshorse.com


SimMuscle 2.2.2
Institute of Physiology
Philipps University of Marburg
norecopa
AMPLITUDE
400
[mV]
Pulse-Duration: 1ms
INTERVAL
50
[ms]
NUMBER OF PULSES
SINGLE
TWIN
TRAIN
STIMULATION
START->
POWER
Zero Adj
FREE
LOCK
LENGTH
FORCE
STORE
CLEAR
UNDO
CHANNEL1 [mV/Div]
CHANNEL2 [mV/Div]
EXIT
SOUND OFF
virtualphysiology.com


rescuecritters.com

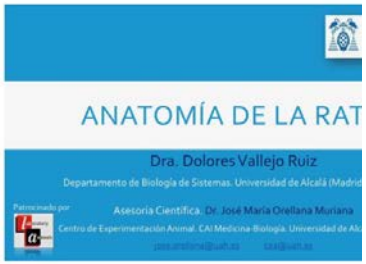

limbsandthings.com

norecopa.no/education-training/films-and-slide-shows

norecopa

Rat s.c. injection
Norecopa | 1,380 views

Rat i.p. injection (method 2)
Norecopa | 1,280 views



Anatomia de la rata
Norecopa | 977 views

Testing anaesthetic depth in the chicken
Norecopa | 598 views

Blood collection from the saphenous vein in the mouse
Norecopa | 6,777 views

Subcutaneous injection in the rat - Technique 1
Norecopa | 2,249 views

Blood san
Norecop

Blood san
Norecop

Blood san
Norecop

Blood sampling from the pig
Norecopa | 3,914 views

Intravenous injection in a rabbit
Norecopa | 2,025 views

Lifting a rabbit
Norecopa | 2,420 views

Subcutaneous injection in the rabbit
Norecopa | 1,479 views

Subcutaneous injection in the chicken
Norecopa | 1,806 views

Immobilisation of the rabbit
Norecopa | 2,072 views

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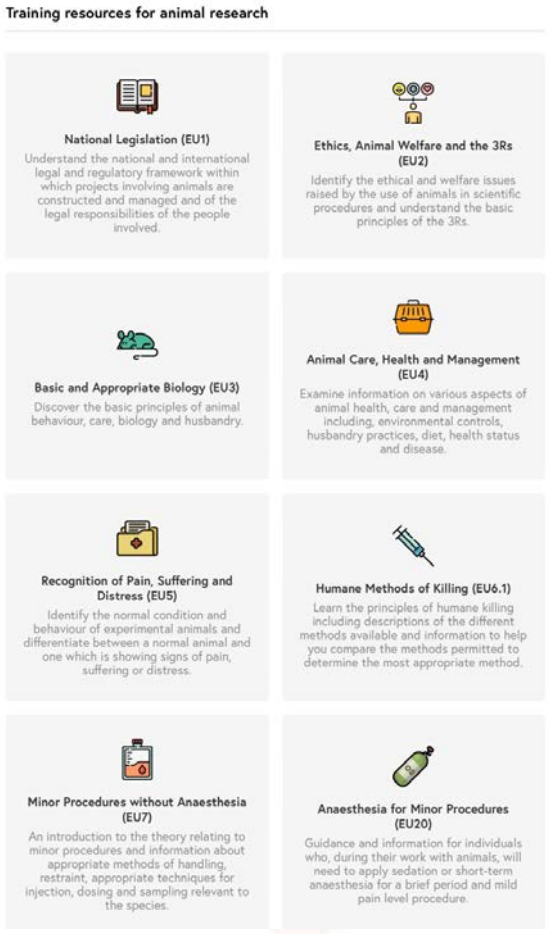
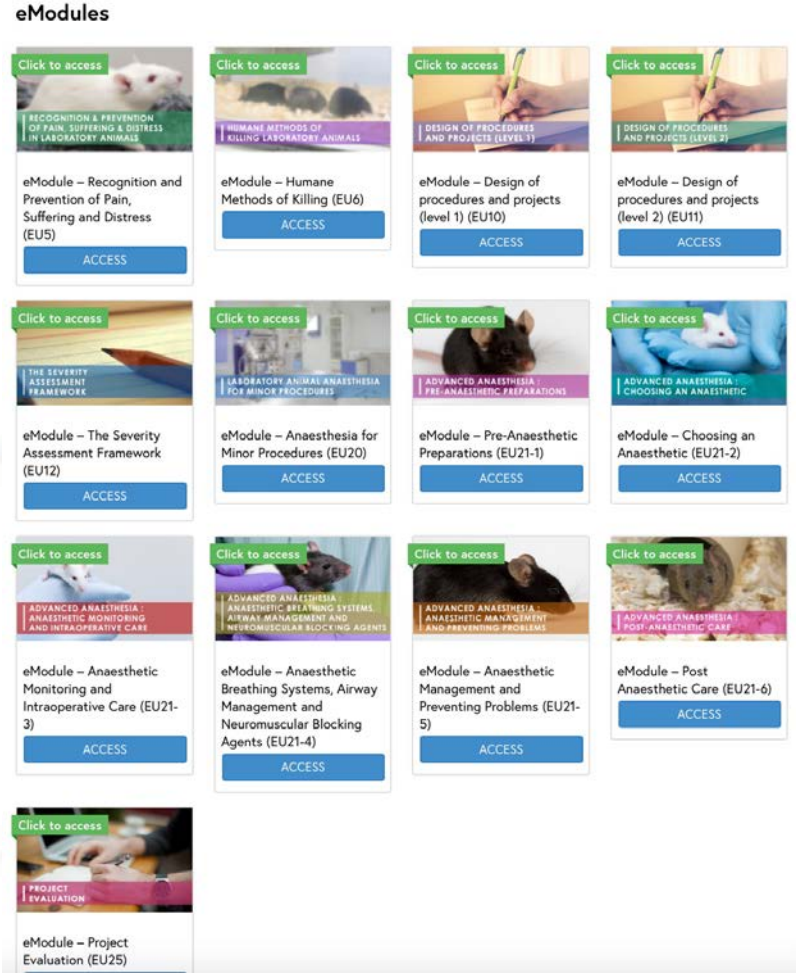
RESEARCH ANIMAL TRAINING

researchanimaltraining.com

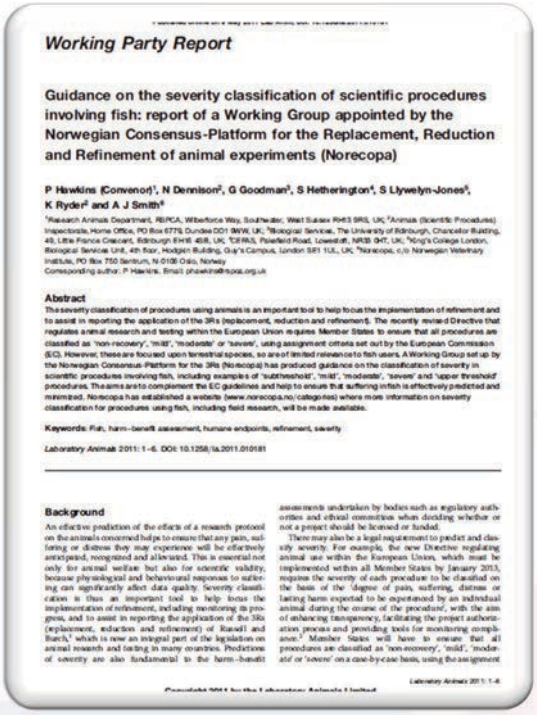
Articles ⌄ eModules ⌄ Log in





From **3R-Guide** (380 guidelines for animal research and testing)

norecopa.no/3r-guide



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 Dennison[2], G Goodman[3], S Hetherington[4], S Llywelyn-Jones[5], K Ryder[2] and A J Smith[6]

[1]Research Animals Department, RSPCA, Wilberforce Way, Southwater, West Sussex RH13 9RS, UK; [2]Animals (Scientific Procedures) Inspectorate, Home Office, PO Box 6779, Dundee DD1 9WW, UK; [3]Biological Services, The University of Edinburgh, Chancellor Building, 49, Little France Crescent, Edinburgh EH16 4SB, UK; [4]SFIRS, Pitsfield Road, Lowestoft, NR33 0HT, UK; [5]King's College London, Biological Services Unit, 4th floor, Hodgkin Building, Guy's Campus, London SE1 1UL, UK; [6]Norecopa, c/o Norwegian Veterinary Institute, PO Box 750 Sentrum, N-0106 Oslo, Norway

Corresponding author: P Hawkins. Email: phawkins@rspca.org.uk

Abstract

The severity classification of procedures using animals is an important tool to help focus the implementation of refinement and 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 (Norecopa) has produced guidance on the classification of severity in scientific procedures involving fish, including examples of 'subthreshold', 'mild', '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.

Keywords: Fish, harm–benefit assessment, humane endpoints, refinement, severity

Laboratory Animals 2011; 1–6. DOI: 10.1258/la.2011.010181

Background

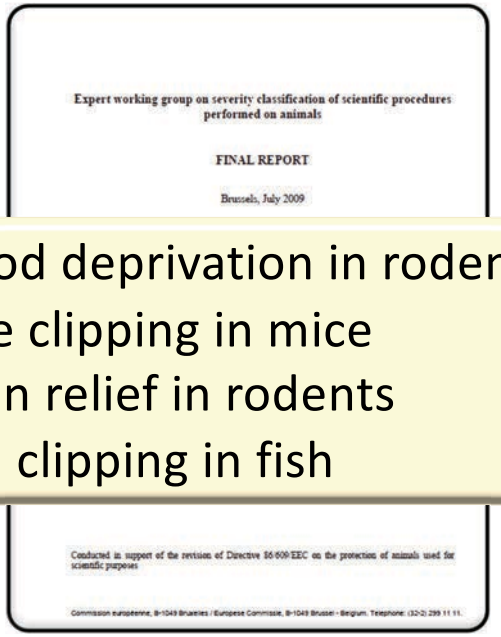
An effective prediction of the effects of a research protocol on the animals concerned helps to ensure that any pain, suffering or distress they may experience will be effectively anticipated, recognized and alleviated. This is essential not only for animal welfare but also for scientific validity, because physiological and behavioural responses to suffering can significantly affect data quality. Severity classification is thus an important tool to help focus the implementation of refinement, including monitoring its progress, and to assist in reporting the application of the 3Rs (replacement, reduction and refinement) of Russell and Burch,[1] which is now an integral part of the legislation on animal research and testing in many countries. Predictions of severity are also fundamental to the harm–benefit assessments undertaken by bodies such as regulatory authorities and ethical committees when deciding whether or not a project should be licensed or funded.

There may also be a legal requirement to predict and classify severity. For example, the new Directive regulating animal use within the European Union, which must be implemented within all Member States by January 2013, requires the severity of each procedure to be classified on the basis of the 'degree of pain, suffering, distress or lasting harm expected to be experienced by an individual animal during the course of the procedure', with the aim of enhancing transparency, facilitating the project authorization process and providing tools for monitoring compliance.[2] Member States will have to ensure that all procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe' on a case-by-case basis, using the assignment

Laboratory Animals 2011; 1–6

Guidance on the severity classification of procedures involving fish

Report from a Working Group
convened by Norecopa



Expert working group on severity classification of scientific procedures performed on animals

FINAL REPORT

Brussels, July 2009

Conducted in support of the revision of Directive 86/609/EEC on the protection of animals used for scientific purposes

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11.

Food deprivation in rodents
Toe clipping in mice
Pain relief in rodents
Fin clipping in fish

http://ec.europa.eu/environment/chemicals/lab_animals/pdf/report_ewg.pdf

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

TextBase:

1,500 books related to LAS:

norecopa.no/textbase

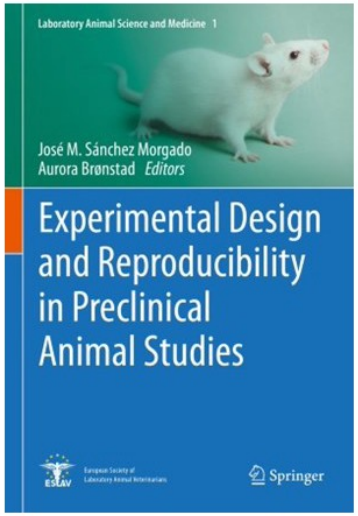
Experimental Design and Reproducibility in Preclinical Animal Studies

By José M. Sánchez Morgado & Aurora Brønstad (Eds.)

Record number: 8619d

This book provides grounds on how to plan and conduct animal experiments that can be reproduced by others. It touches on factors that may impact the reproducibility of animal studies including: the animal genetic background, the animal microbial flora, environmental and physiological variables affecting the animal, animal welfare, statistics and experimental design, systematic reviews of animal studies, and the publishing process.

The book addresses advanced undergraduates, graduate students and all scientists working with animals.



norecopa.no/textbase/experimental-design-and-reproducibility-in-preclinical-animal-studies

We have a "reproducibility crisis" in science...

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

norecopa.no/concerns

Reporting

Planning

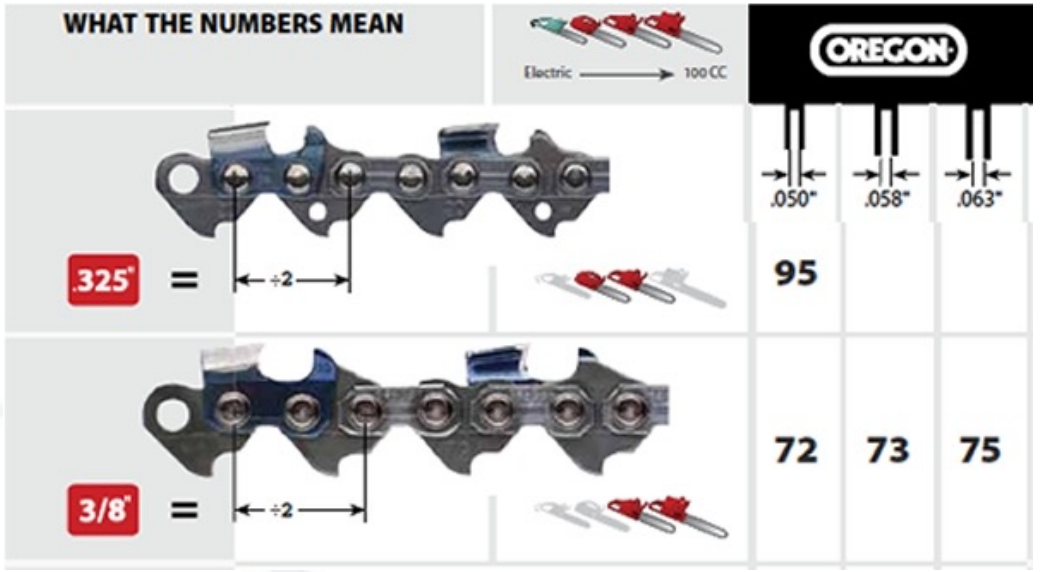
We cannot improve our research by

better reporting alone...

reddit.com

Norecopa: PREPARE for better Science

The easy parts of design and reporting:



arborist101.com

- Chainsaw
  - Blade characteristics
  - Sparkplug type
  - Petrol/oil mixture
  - Service history
- Angle of cut in tree
- Length of tree logs

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Critical issues behind the scenes that may not get reported:

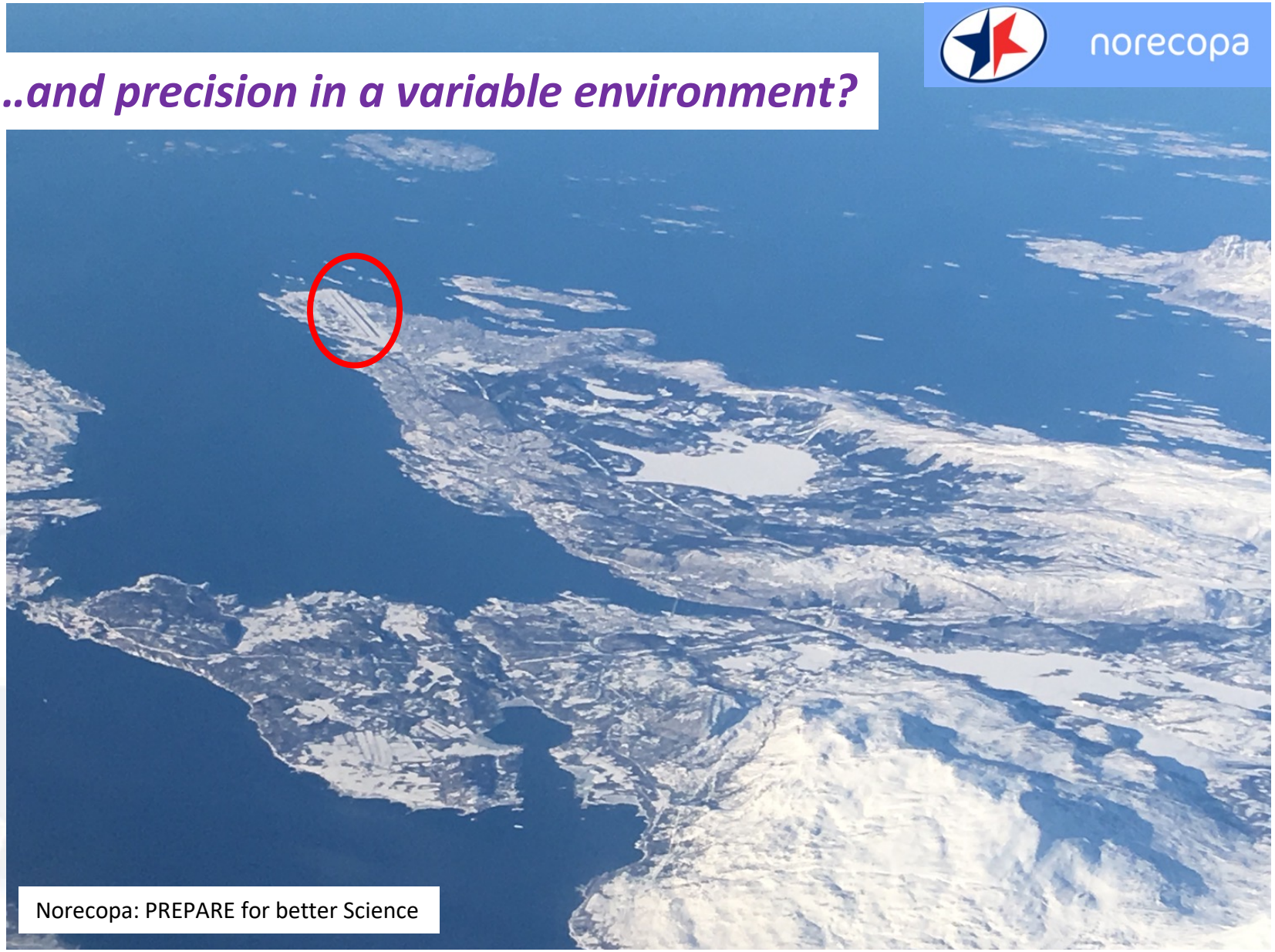
- Experience of the workers
- Inspection for signs of rot and to decide felling direction
- Additional equipment (winch, chains, straps, wedges)
- Routines and equipment for sharpening the chain
- Clearing-up and transport of logs
- Health and safety precautions – clothing, onlookers
- **Division of labour and costs**

Starts long before the actual work.

How do others achieve reproducibility?

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

…and precision in a variable environment?



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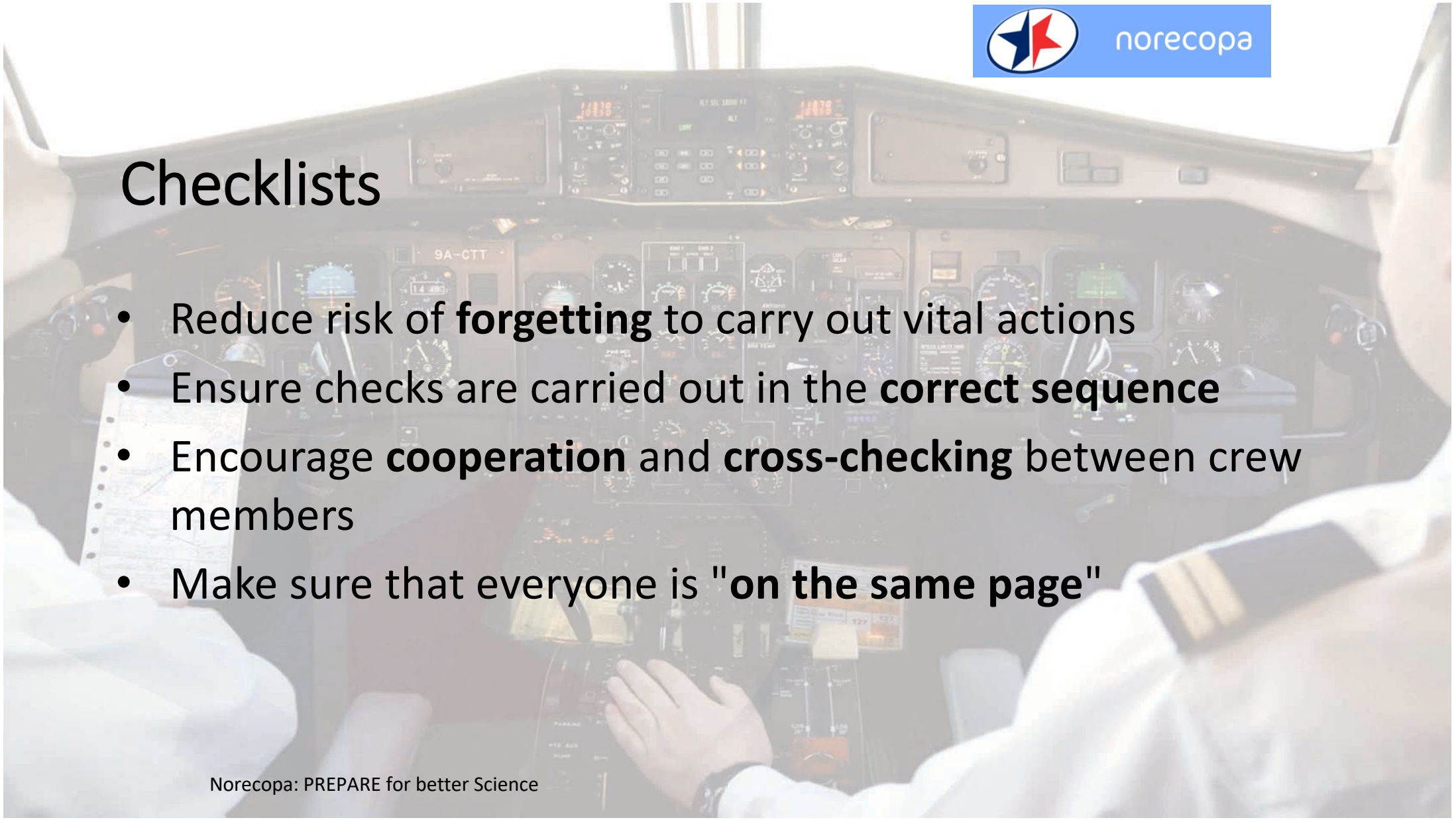
10-15 checklists even on short routine flights



Checklists

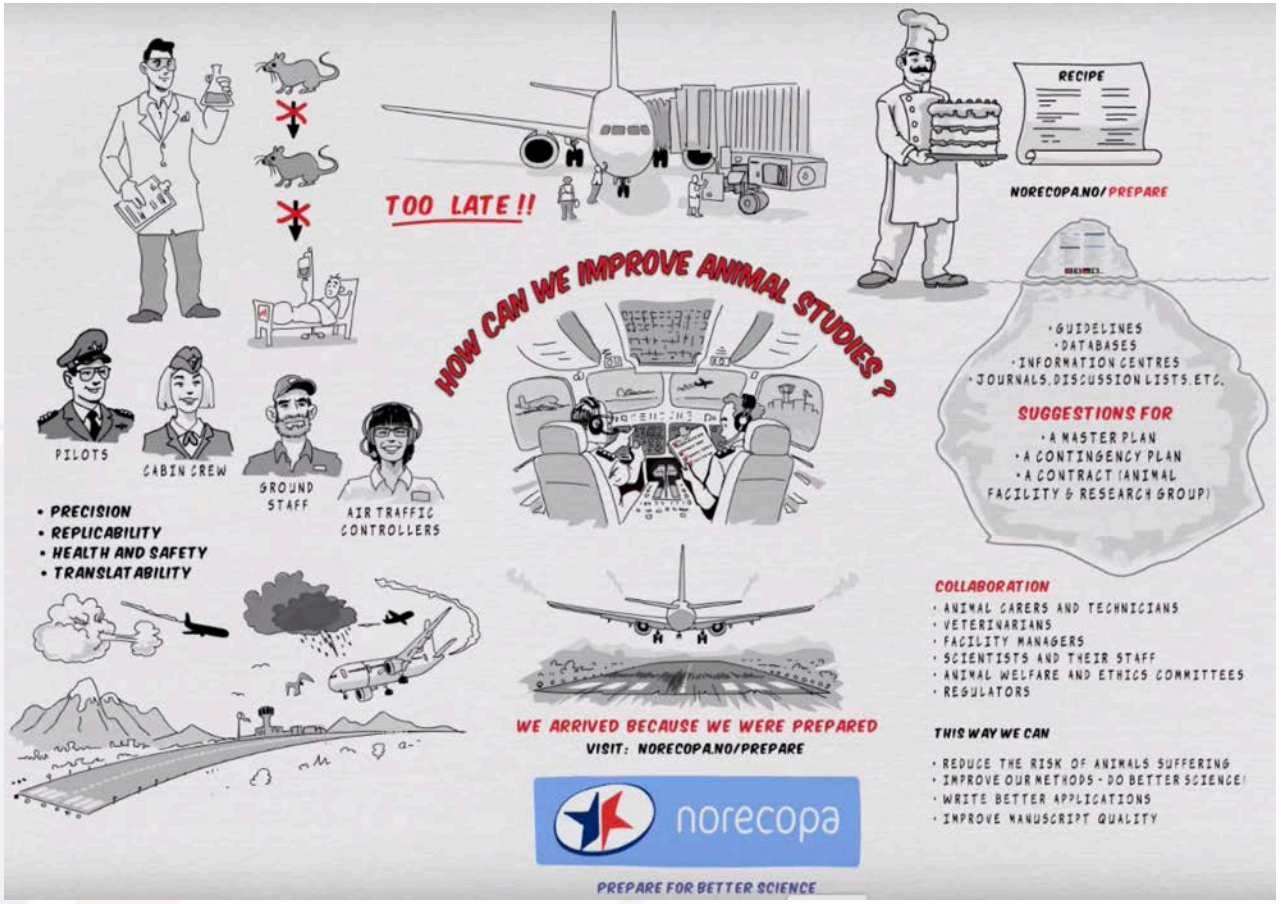
- Reduce risk of **forgetting** to carry out vital actions
- Ensure checks are carried out in the **correct sequence**
- Encourage **cooperation** and **cross-checking** between crew members
- Make sure that everyone is "**on the same page**"

Too late to read the checklists when you have ARRIVEd!

colourbox.com

norecopa.no/PREPARE/film

3-minute cartoon film



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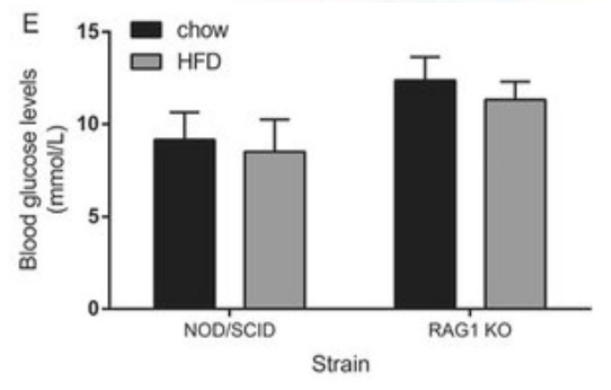
The scientist



The mouse

Breeding
New social groups
Transportation
Acclimation to research facility
Allocation to experimental group
Adaptation to new diet
Handling and immobilisation

Blood sampling

often also:
injections, gavaging, surgery
pain and distress
developing illness and death

Stress caused by capture and handling

INDEPENDENT

News › Science

Scores of scientific studies based on mice thrown into doubt because they wer

Mice picl 't act naturally

Ian Johnstor

nc3rs.org.uk/3rs-resources/mouse-handling

Artefacts caused by poor administration techniques

Photo: NMBU

- *Are you sure that your injection ends up in the same place each time?*
- *Are the injections painful?*
- *Are they realistic? (intramuscular injections in small animals)*

Disposable needles are designed to be used only once!

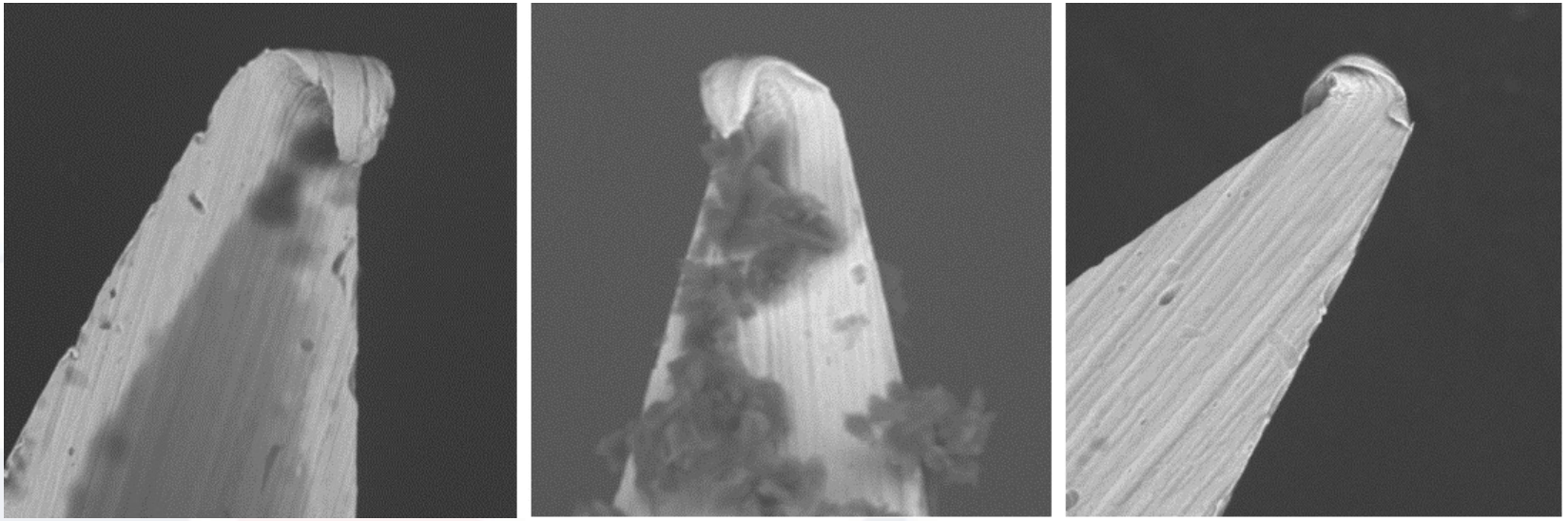


Photo: AstraZeneca

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

'A simple' case: a researcher wants a blood sample

medipoint.com/html/for_use_on_mice.html

theodora.com/rodent_laboratory/blood_collection.html

vimeo.com/486368886

photo:NMBU

The best blood sampling techniques are those where you can:

- ✓ see the blood vessel
- ✓ regulate the amount of blood you remove
- ✓ stop the bleeding easily (including internal bleeding)
- ✓ avoid damage to the surrounding tissue
- ✓ collect samples rapidly, to avoid artefacts due to mechanical stress, temperature changes, differing lengths of sampling time

While we are waiting for the scientific evidence…

Carol M. Newton (1925-2014)

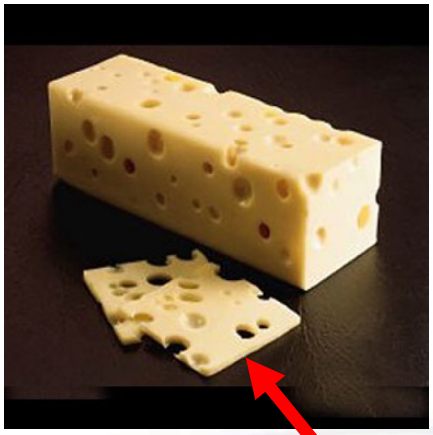
National Library of Medicine

The three S's

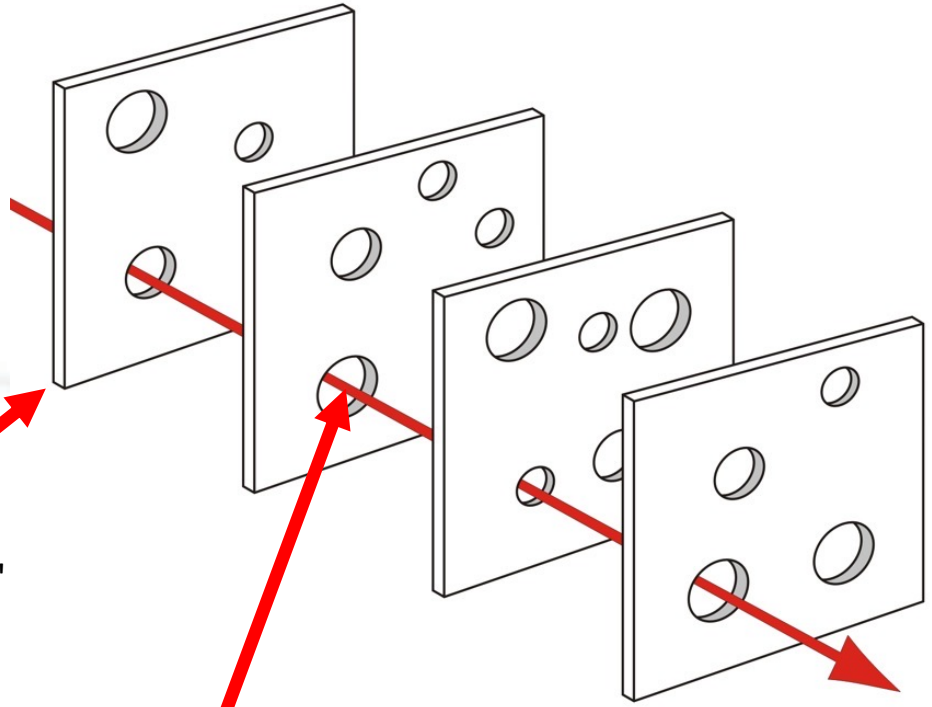
- *Good Science*
- *Good Sense*
- *Good Sensibilities*

https://norecopa.no/3S

Threat and Error Management



eaugallecheese.com/Swiss-Cheese



"Layer of defence"
or redundancy

Weakness / hazard

Loss

wikipedia.org/wiki/Swiss_cheese_model

Contingency and redundancy

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

Photo: NMBU

Culture of Care

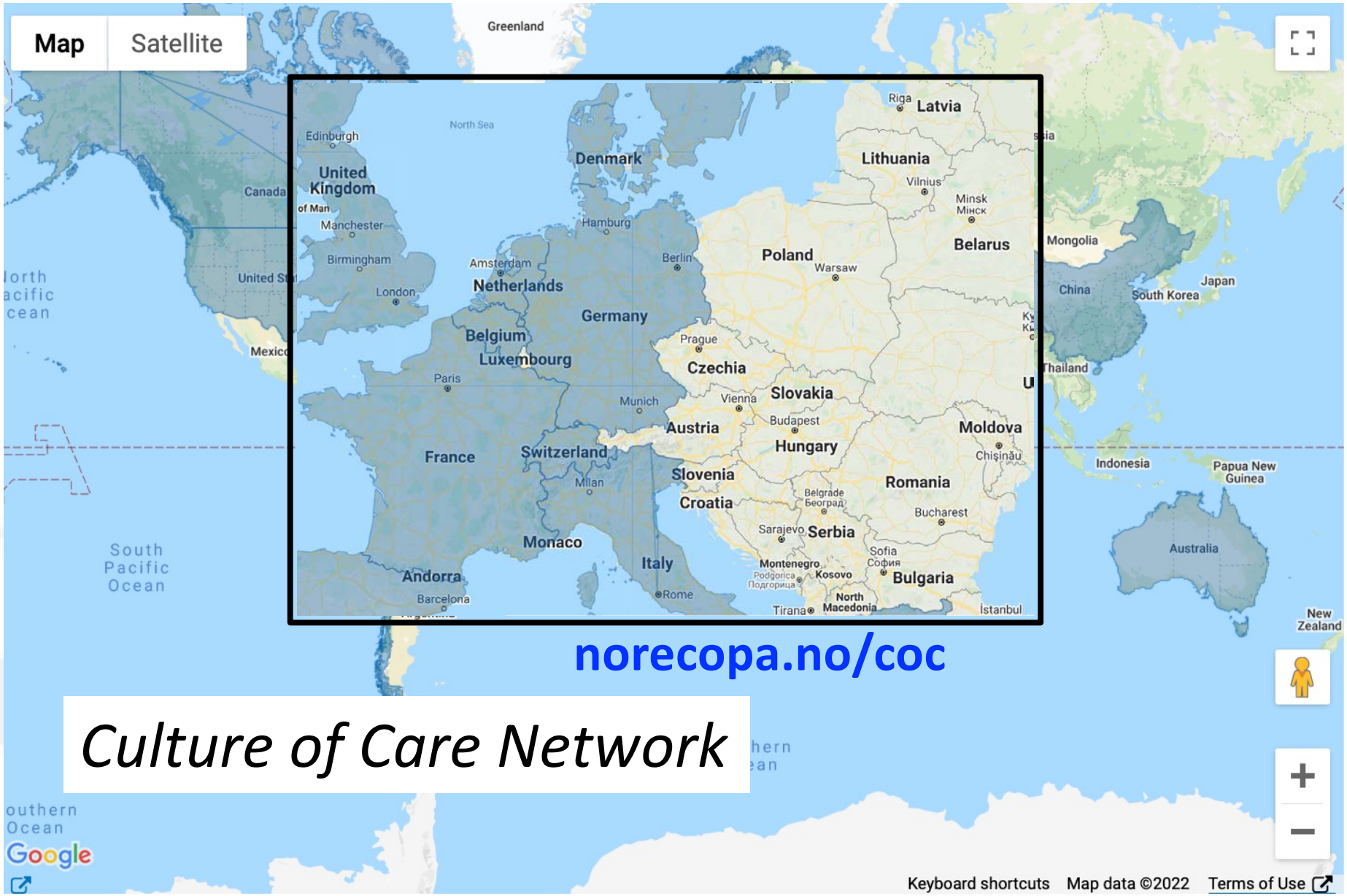
The International Culture of Care Network

norecopa.no/coc

A demonstrable commitment, throughout the establishment, to improving:

- animal welfare
- scientific quality
- care of staff
- transparency for all stakeholders, including the public

It goes beyond simply complying with the law!



norecopa.no/coc

Culture of Care Network

"because we've always done it that way"

"as often as necessary"

"there are no alternatives"

Closely related to a culture of care is the concept of

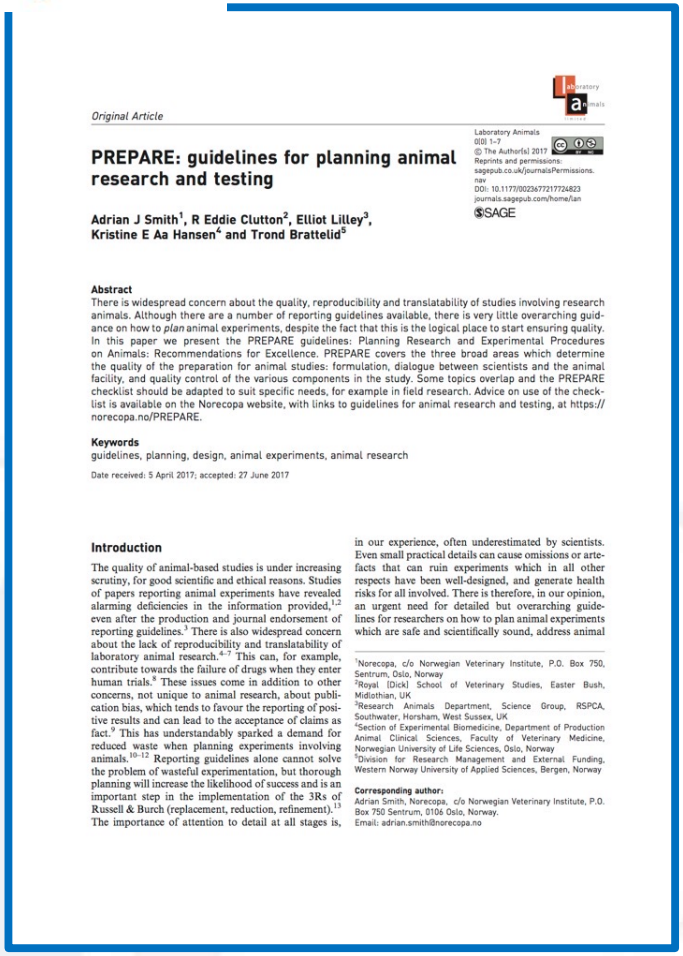
a **Culture of Challenge** (Louhimies, 2015)**.**

Look for the acceptable, rather than choosing the accepted.

PREPARE encourages scientists to collaborate with animal carers and 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
- lack of involvement creates anxiety, depression and opposition to animal research, as well as limiting creativity which might improve the experiments

Prepare



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
0(0) 1–7

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

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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[2]Royal (Dick) School of Veterinary Studies, Easter Bush, Midlothian, UK
[3]Research Animals Department, Science Group, RSPCA, Southwater, Horsham, West Sussex, UK
[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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Norecopa: PREPARE for better Science

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https://doi.org/10.1177/0023677217724823

Over 22,000 downloads from the journal website so far

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 typically highlighted in reporting guidelines

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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.

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Three Rs!

Topic	Recommendation
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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.

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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.

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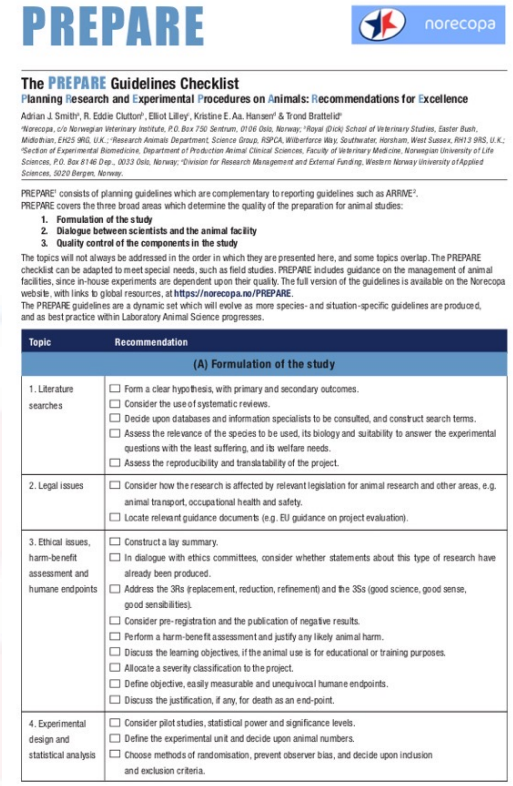

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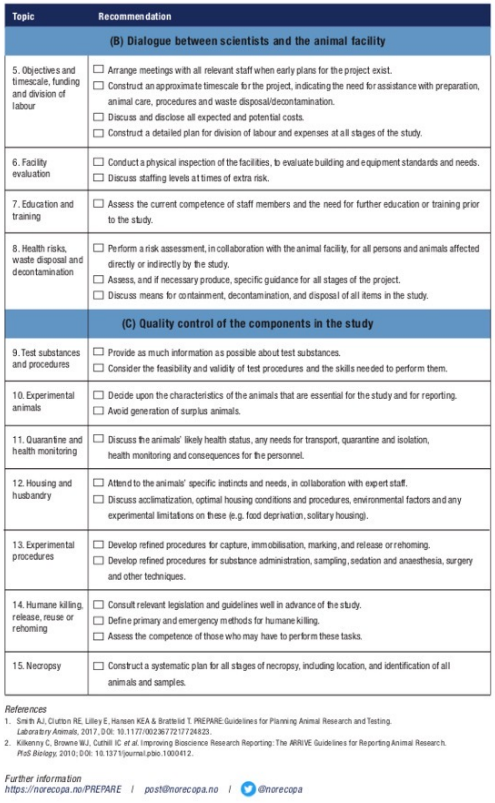

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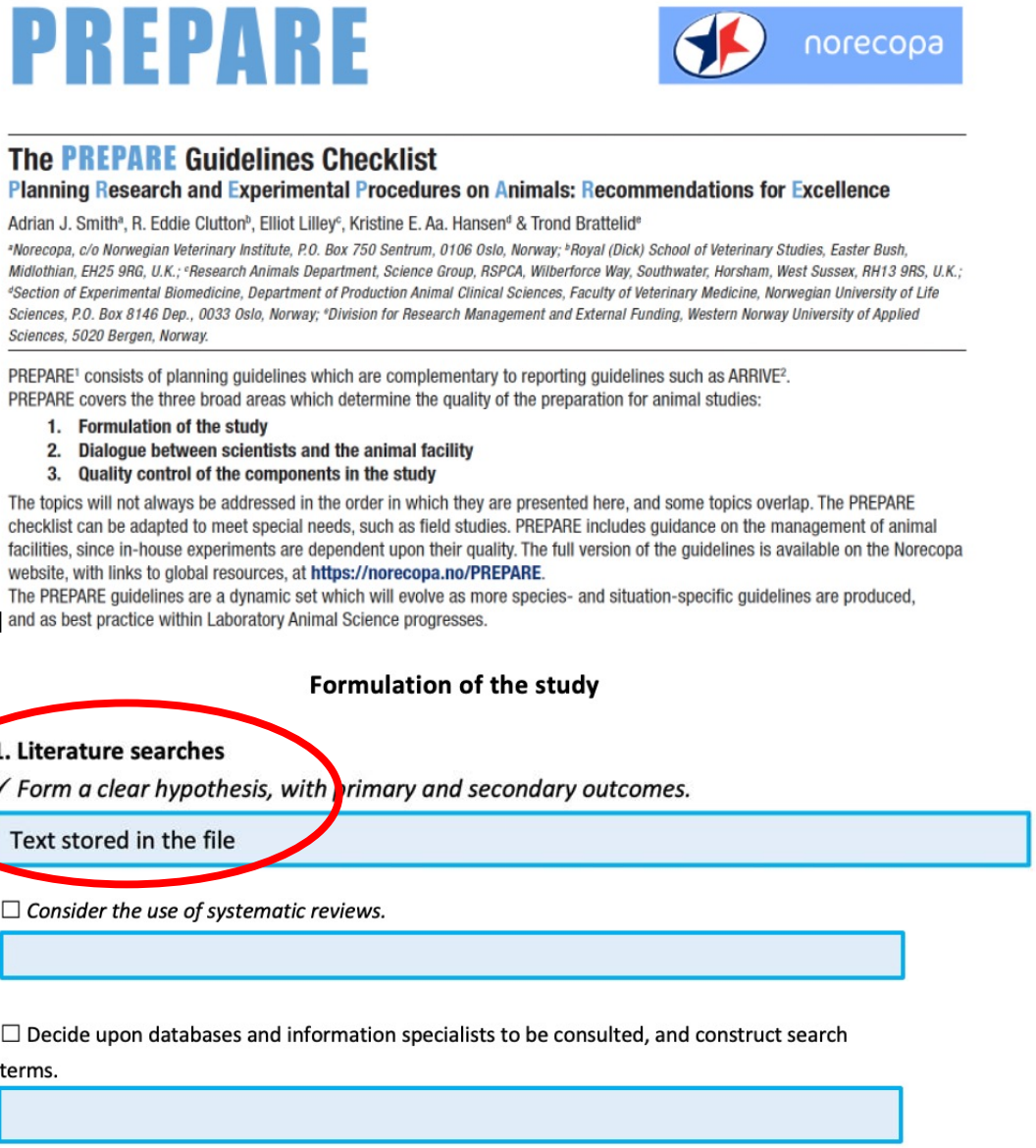

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Formulation of the study

1. Literature searches

✓ *Form a clear hypothesis, with primary and secondary outcomes.*

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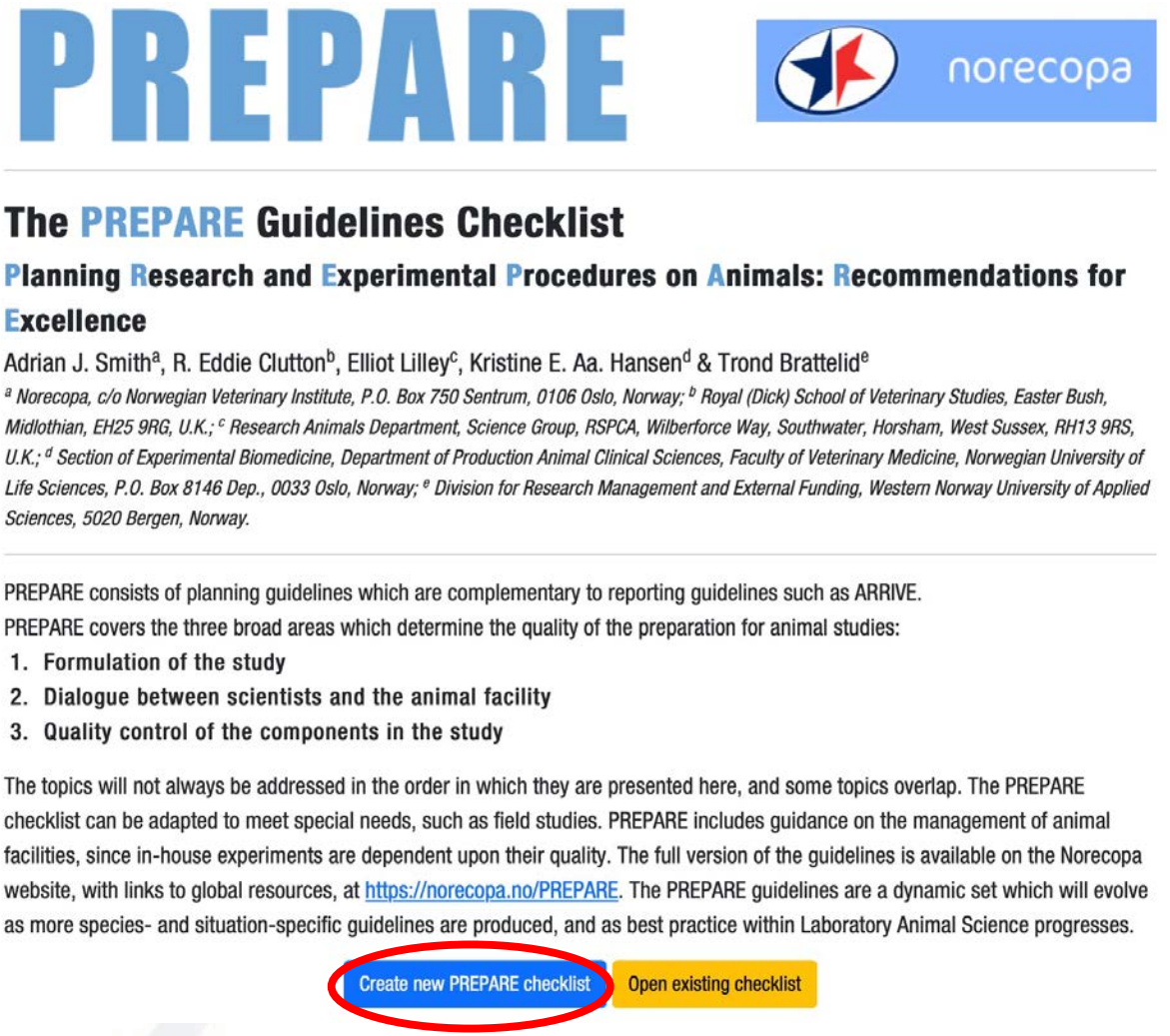

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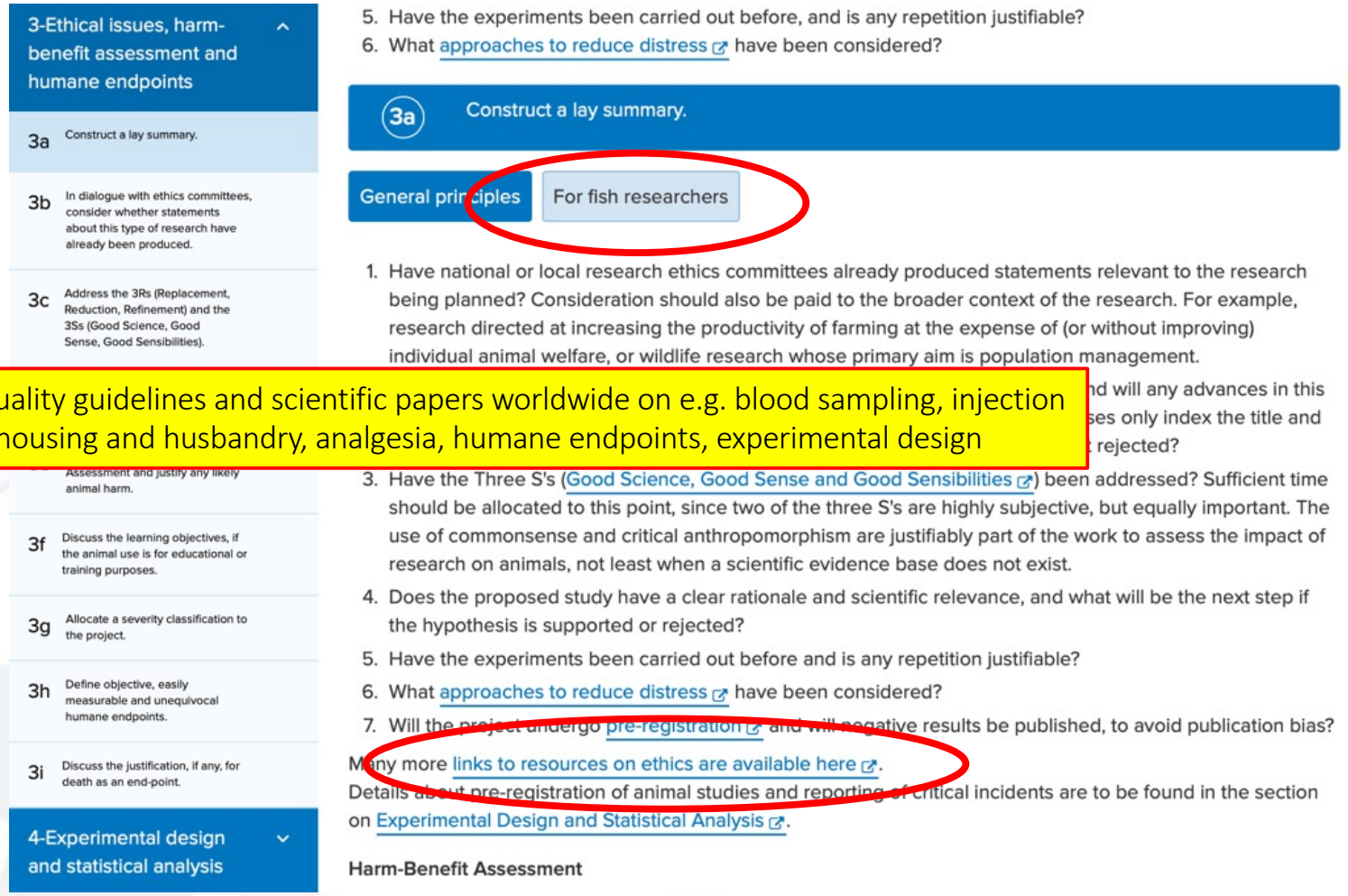

Links to quality guidelines and scientific papers worldwide on e.g. blood sampling, injection volumes, housing and husbandry, analgesia, humane endpoints, experimental design

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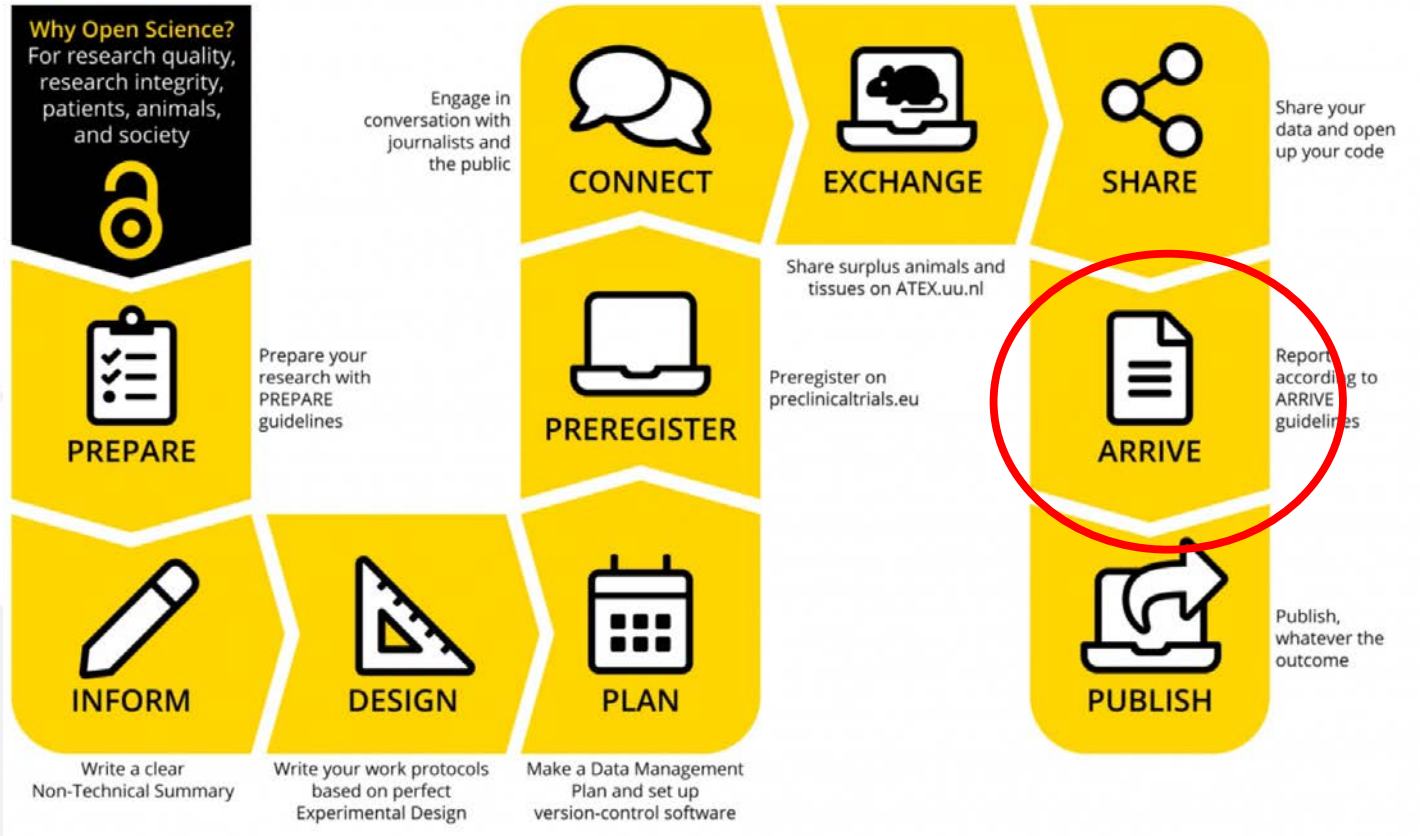

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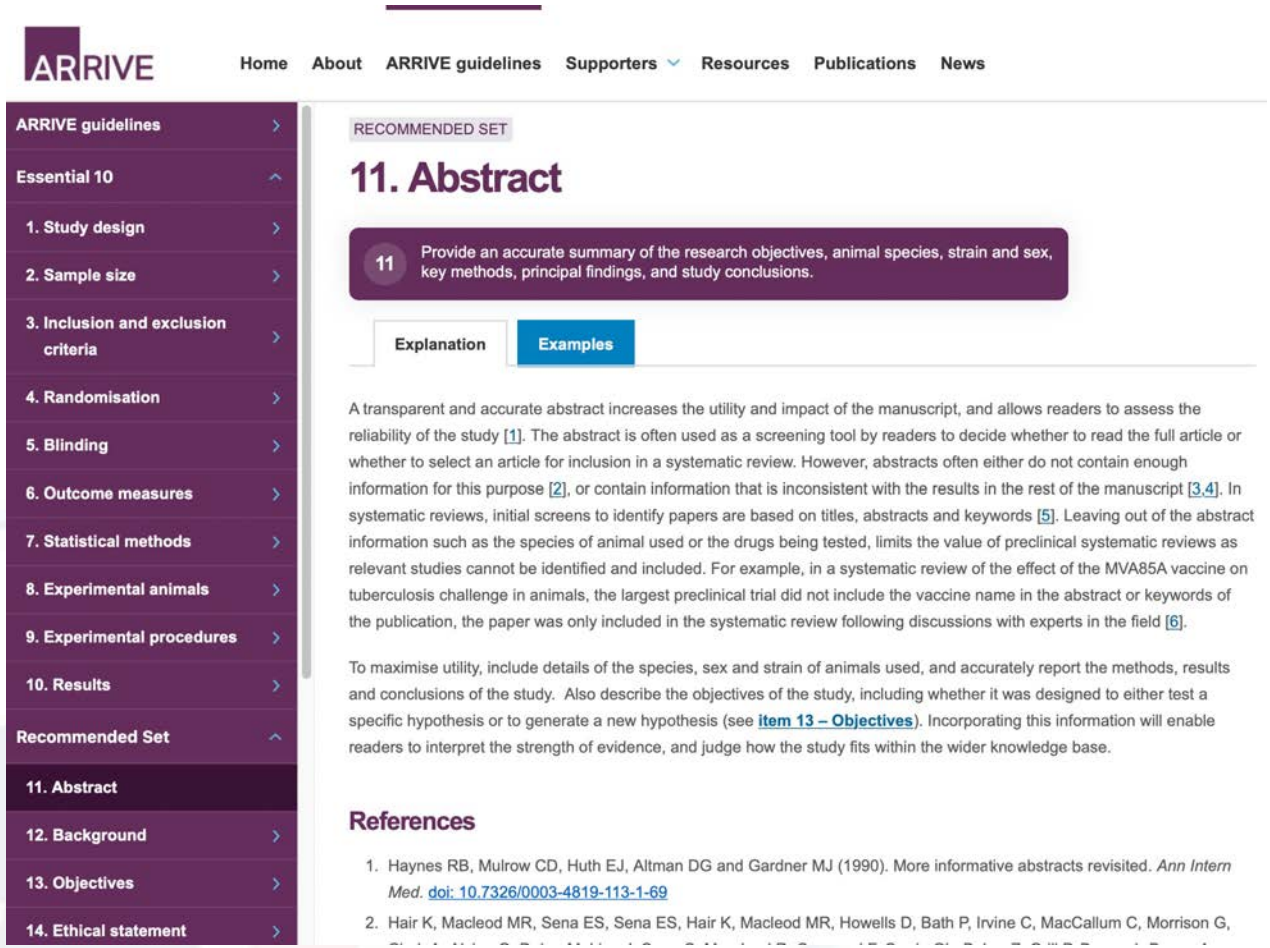

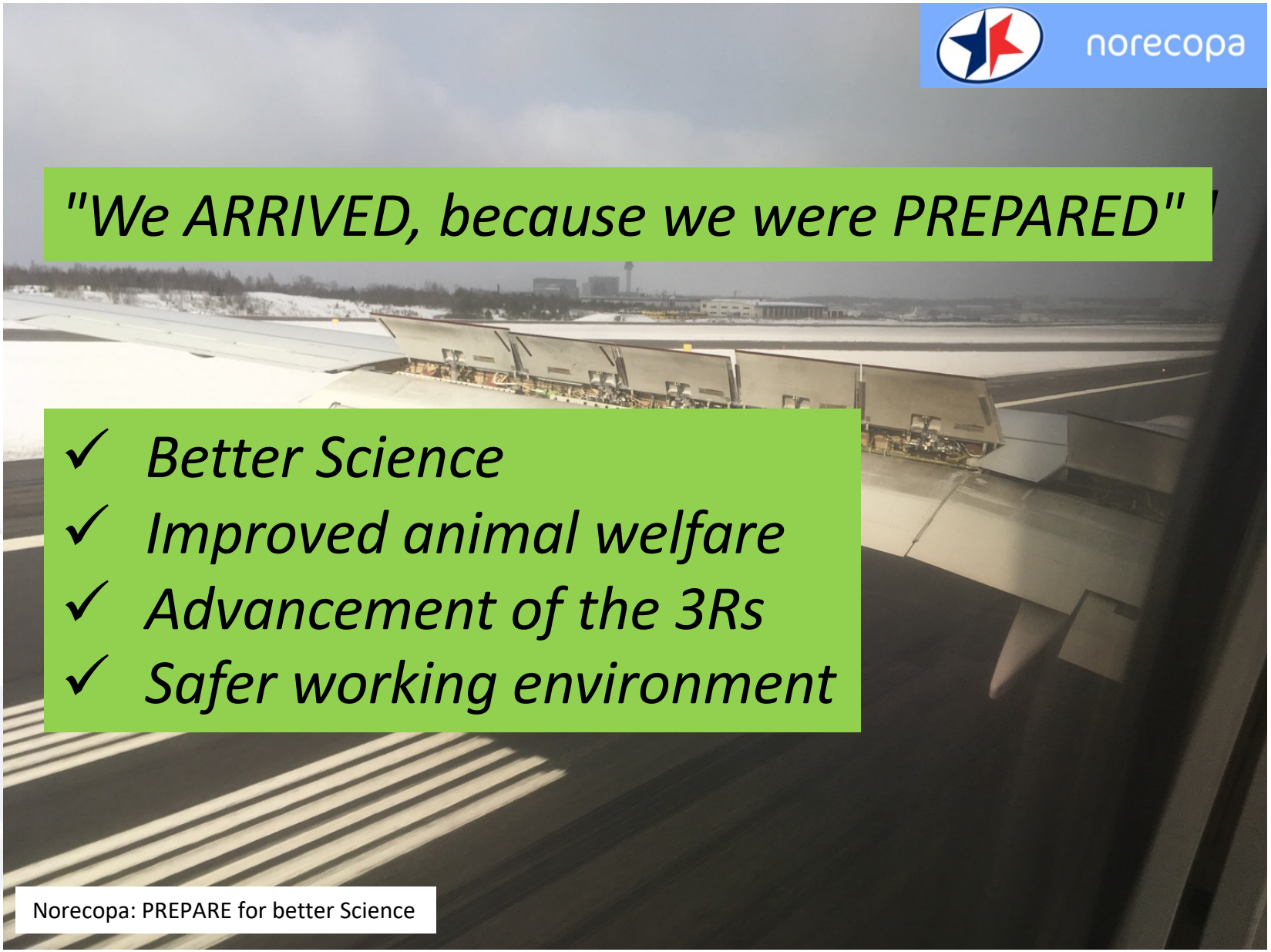
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3R improvements are often not highlighted in the scientific literature

http://www.theodora.com/rodent_laboratory/blood_collection.html

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SCID-Hu mice immunized with a pneumococcal vaccine produce specific human antibodies and show increased resistance to infection.

Saphenous vein puncture for blood sampling of the mouse, rat, hamster, gerbil, guineapig, ferret and mink

Annelise Hem[1], Adrian J. Smith[2] & Per Solberg[1]

[1]Laboratory Animal Unit, National Institute of Public Health, PO Box 4404 Torshov, N-0403 Oslo and
[2]Laboratory Animal Unit, Norwegian School of Veterinary Science, PO Box 8146 Dep., N-0033 Oslo,

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Summary

A method is described for blood collection from the lateral saphenous vein. This enables rapid sampling, which if necessary can be repeated from the same site without a need for new puncture wounds. The method is a humane and practical alternative to cardiac and retro-orbital puncture, in species where venepuncture has traditionally been regarded as problematic.

Keywords Saphenous vein; blood sampling; mouse; rat; hamster; gerbil; guineapig; rodent; ferret; mink

The title and summary are critical, because they are often the only parts that are indexed by databases.

Not necessarily a high-impact journal.

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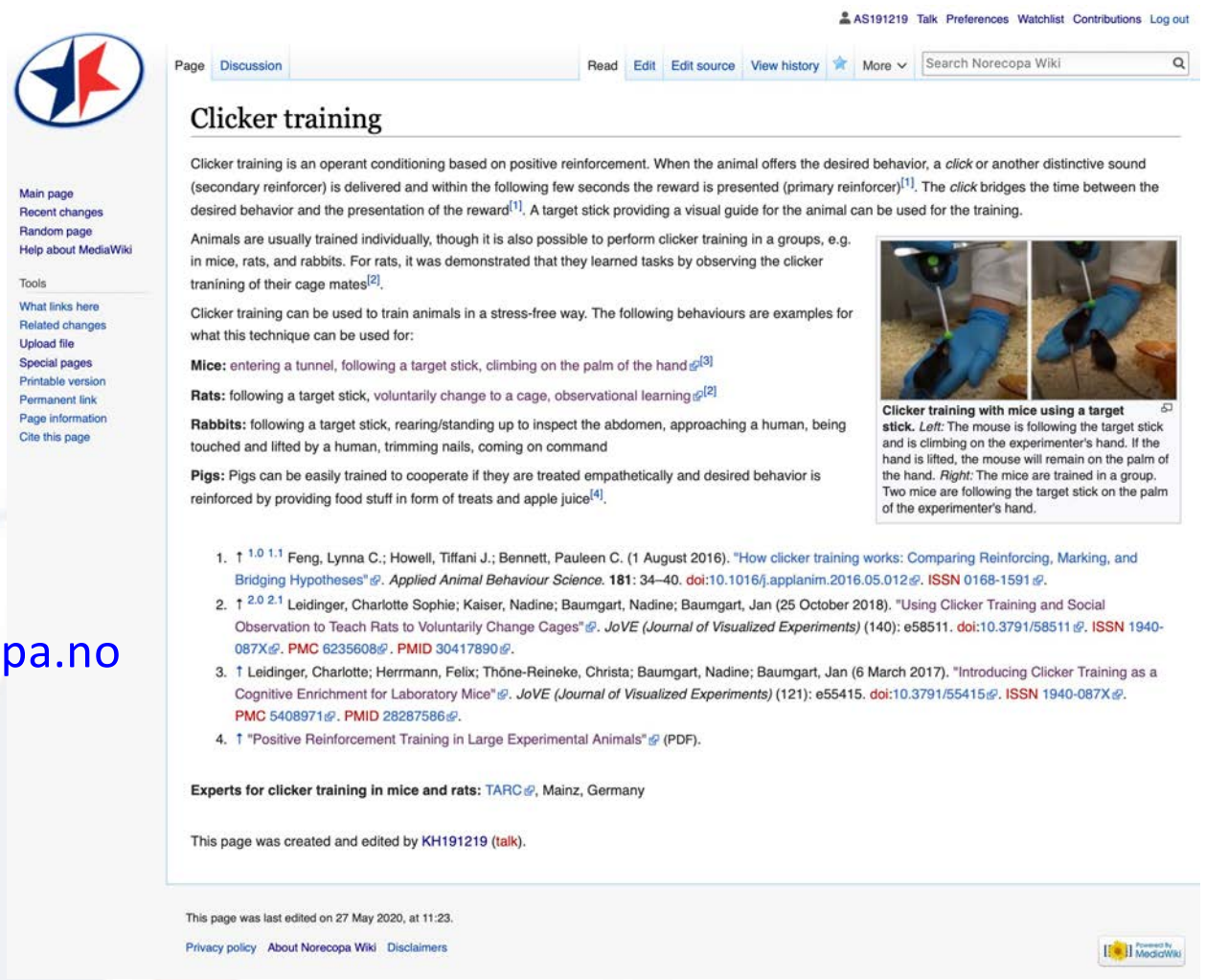

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Clicker training

Clicker training is an operant conditioning based on positive reinforcement. When the animal offers the desired behavior, a *click* or another distinctive sound (secondary reinforcer) is delivered and within the following few seconds the reward is presented (primary reinforcer)[1]. The *click* bridges the time between the desired behavior and the presentation of the reward[1]. A target stick providing a visual guide for the animal can be used for the training.

Animals are usually trained individually, though it is also possible to perform clicker training in a groups, e.g. in mice, rats, and rabbits. For rats, it was demonstrated that they learned tasks by observing the clicker tranining of their cage mates[2].

Clicker training can be used to train animals in a stress-free way. The following behaviours are examples for what this technique can be used for:

Mice: entering a tunnel, following a target stick, climbing on the palm of the hand[3]

Rats: following a target stick, voluntarily change to a cage, observational learning[2]

Rabbits: following a target stick, rearing/standing up to inspect the abdomen, approaching a human, being touched and lifted by a human, trimming nails, coming on command

Pigs: Pigs can be easily trained to cooperate if they are treated empathetically and desired behavior is reinforced by providing food stuff in form of treats and apple juice[4].

Clicker training with mice using a target stick. *Left:* The mouse is following the target stick and is climbing on the experimenter's hand. If the hand is lifted, the mouse will remain on the palm of the hand. *Right:* The mice are trained in a group. Two mice are following the target stick on the palm of the experimenter's hand.

1. ↑ [1.0] [1.1] Feng, Lynna C.; Howell, Tiffani J.; Bennett, Pauleen C. (1 August 2016). "How clicker training works: Comparing Reinforcing, Marking, and Bridging Hypotheses". *Applied Animal Behaviour Science*. **181**: 34–40. doi:10.1016/j.applanim.2016.05.012. ISSN 0168-1591.
2. ↑ [2.0] [2.1] Leidinger, Charlotte Sophie; Kaiser, Nadine; Baumgart, Nadine; Baumgart, Jan (25 October 2018). "Using Clicker Training and Social Observation to Teach Rats to Voluntarily Change Cages". *JoVE (Journal of Visualized Experiments)* (140): e58511. doi:10.3791/58511. ISSN 1940-087X. PMC 6235608. PMID 30417890.
3. ↑ Leidinger, Charlotte; Herrmann, Felix; Thöne-Reineke, Christa; Baumgart, Nadine; Baumgart, Jan (6 March 2017). "Introducing Clicker Training as a Cognitive Enrichment for Laboratory Mice". *JoVE (Journal of Visualized Experiments)* (121): e55415. doi:10.3791/55415. ISSN 1940-087X. PMC 5408971. PMID 28287586.
4. ↑ "Positive Reinforcement Training in Large Experimental Animals" (PDF).

Experts for clicker training in mice and rats: TARC, Mainz, Germany

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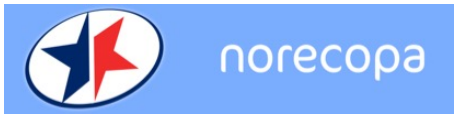

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- Blood sampling of pigs
- Blood sampling of rainbow trout
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- Contingency plans
- Decapitation
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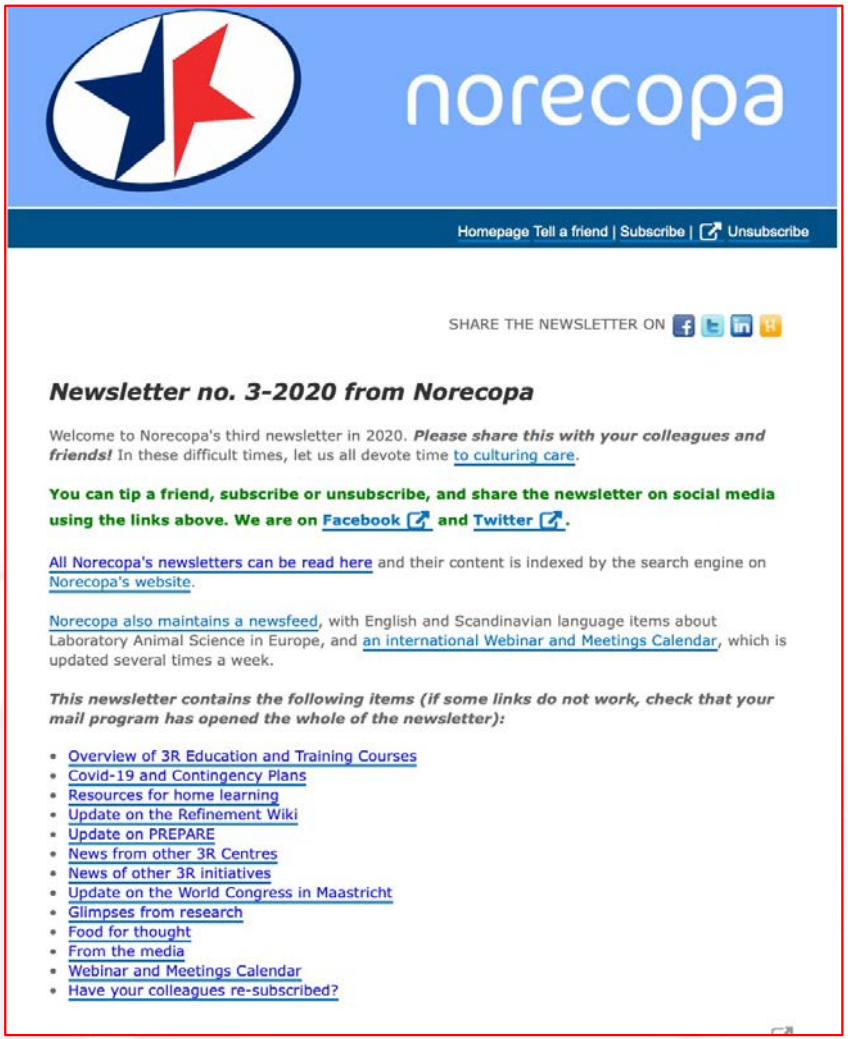

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- Norwegian Animal Protection Alliance (Dyrevernalliansen)
- Novo Nordisk
- Sanofi
- Scottish Accreditation Board (SAB)
- Stiansen Foundation
- Universities Federation for Animal Welfare (UFAW)
- US Department of Agriculture (USDA)

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