

The PREPARE Guidelines for Planning Animal Research and Testing

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norecopa.no

International consensus meetings

Harmonisation of the Care and Use of:

Fish (2005)

Wildlife (2008)

Fish (2009)

Agricultural animals (2012)

Wildlife 26-27 October 2017

[*norecopa.no/meetings*](http://norecopa.no/meetings)

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

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PREPARE utilises the resources on norecopa.no

The screenshot shows the norecopa.no website. At the top, there is a blue header with the norecopa logo (a stylized star) and the text "norecopa". To the right of the logo, there are links for "NORSK" and "ENGLISH". A search bar with the text "Search:" and a magnifying glass icon is highlighted with a red circle. Below the header, there is a navigation menu with links: "About Norecopa", "Alternatives", "Databases & Guidelines", "Education & training", "Legislation", "Meetings", "News", "Other resources", "Species", and "Feedback". Below the navigation menu, there is a list of topics: "Anaesthesia and analgesia", "Animal facilities", "Animal welfare organisations", "Blood sampling", "Email discussion lists", "Environmental enrichment", "Ethics", "Experimental design and statistical analysis", "Harm-Benefit Assessment", "Health monitoring", "Journals", "Organisations", "Severity classification", "Suppliers", and "Systematic reviews". Below the list of topics, there is a search bar with the text "Search all Norecopa's databases and webpages simultaneously:" and a magnifying glass icon. To the right of the search bar, there are social media icons for Facebook, Twitter, Email, and a plus sign. Below the search bar, there is a breadcrumb trail: "norecopa.no / Other resources /".

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)

6,000 webpages
>85,000 links
22,500 unique links
<4% dead links

There are many guidelines for *reporting* animal studies

- Öbrink & Waller, 1996 (in *Försöksdjurskunskap*)
- Jane Smith *et al.*, 1997
- Adrian Smith & Trond Brattelid, 2000 (fish)
- 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 List, 2010 (SYRCLE)
- Institute for Laboratory Animal Research, NRC, 2011
- Instructions to authors, in many journals
e.g. Nature's Reporting Checklist

NATURE | NEWS



Swiss survey highlights potential flaws in animal studies

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

Ramin Skibba

20 December 2016

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

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

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

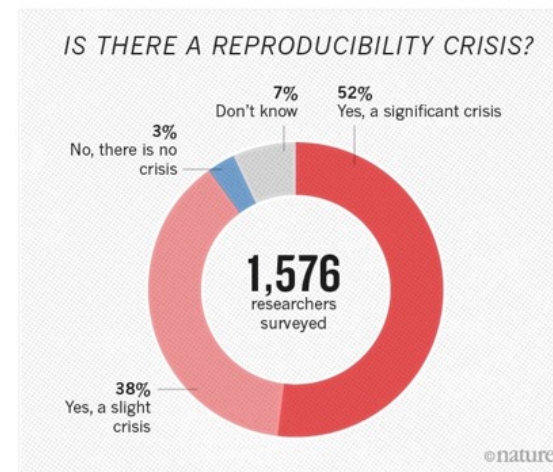
NATURE | NEWS FEATURE

1,500 scientists lift the lid on reproducibility

Survey sheds light on the 'crisis' rocking research.

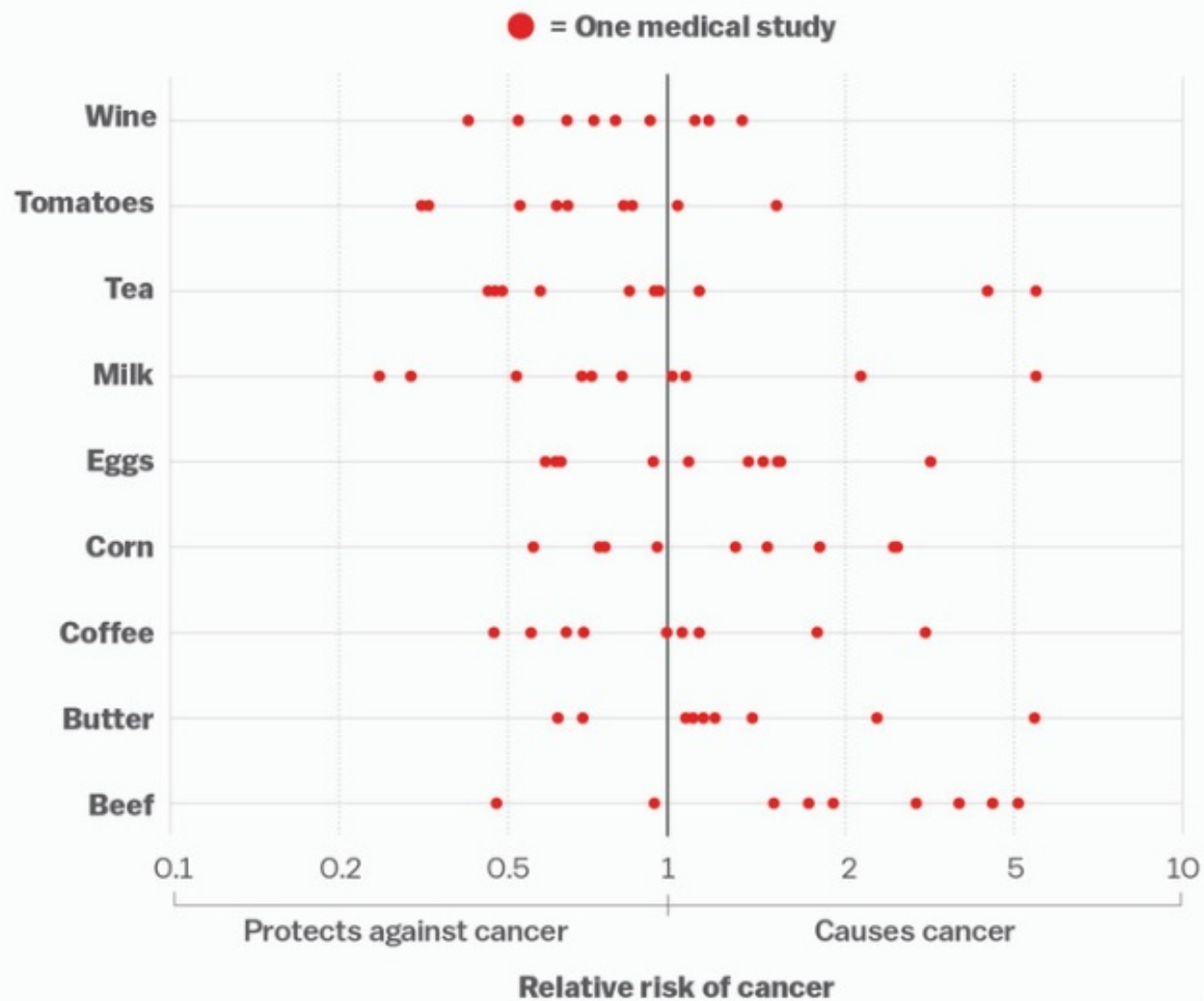
Monya Baker

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 that emerged from Nature's survey of 1,576 researchers who took a brief online questionnaire on reproducibility in research.

Everything we eat both causes and prevents cancer



SOURCE: Schoenfeld and Ioannidis, *American Journal of Clinical Nutrition*

Vox



Missing mice: gaps in data plague animal research

Reports of hundreds of biomedical experiments lack essential information.

Monya Baker

05 January 2016

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Two studies have unveiled widespread flaws in the reporting of animal experiments — the latest in a series of papers to criticize [shoddy biomedical research](#).

Whereas reports of clinical trials in major medical journals routinely state how many patients die or drop out of analysis during the course of a study, animal studies generally fail to report this figure — or drop animals without saying why, according to a team led by Ulrich Dirnagl at the Charité Medical University in Berlin. That lapse could significantly bias results, the team reports in the journal *PLoS Biology*¹.

In a second study in the same journal², a team led by John Ioannidis, an epidemiologist at Stanford University in California who has repeatedly called for more reproducible and transparent research, criticizes the lack of data availability and detailed protocols in biomedical papers.

Despite journal endorsement of reporting guidelines, there is not widespread compliance

Swiss study (2016)*

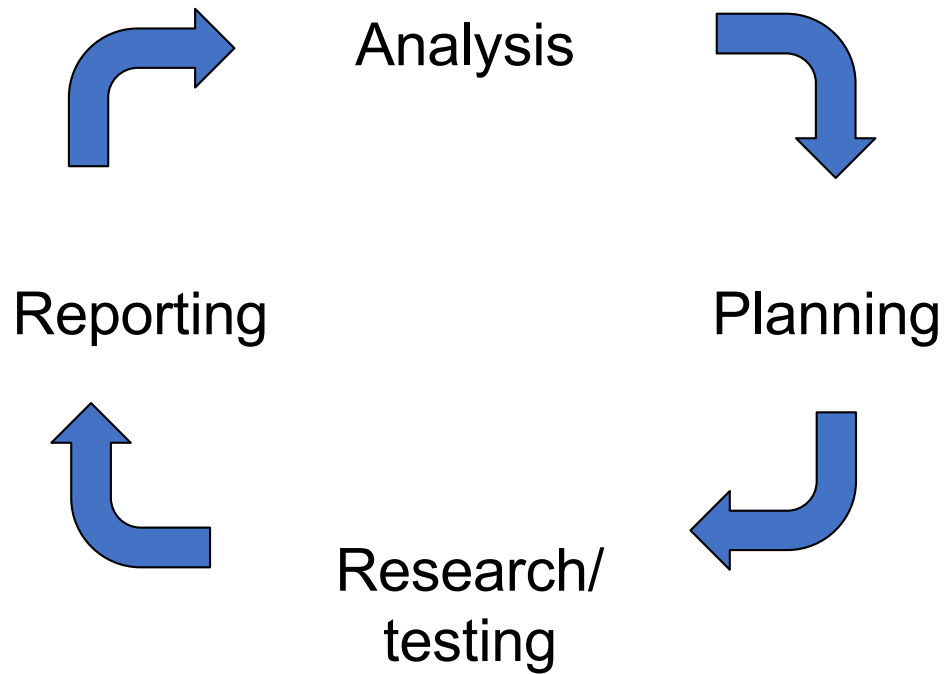
more than half of the researchers using journals which had endorsed ARRIVE (2010) had never heard of the guidelines

Possible reasons for failure to comply with reporting guidelines**

- Low level of detail in the Instructions for Authors
- Lack of attention to this by referees
- Focus on regulatory compliance rather than on animal welfare issues

* Reichlin, Vogt & Wurbel: The Researchers' View of Scientific Rigor-Survey on the Conduct and Reporting of In Vivo Research. *PLoS One*, 2016.

** Martins & Franco: A Critical Look at Biomedical Journals' Policies on Animal Research by Use of a Novel Tool: The EXEMPLAR Scale. *Animals*, 2015.



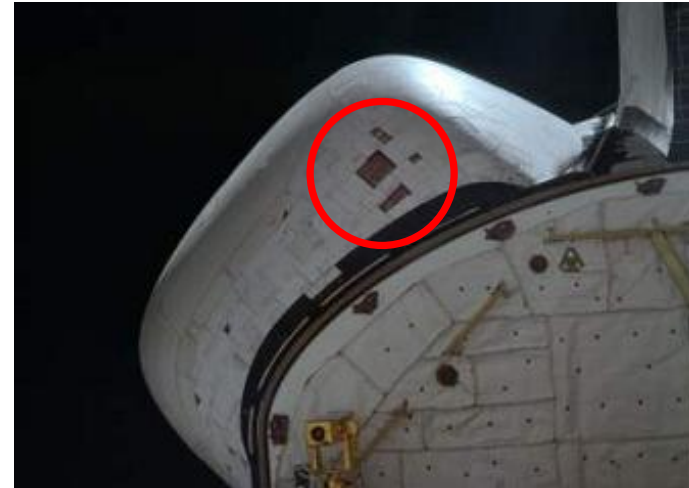
Space Shuttle, NASA

Identify and ensure the quality of (at least) the **critical points** in the experiment: critical for animal welfare and scientific value

1) Columbia



Photo: gettyimages.no

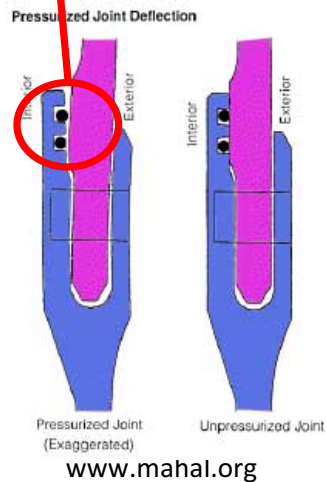
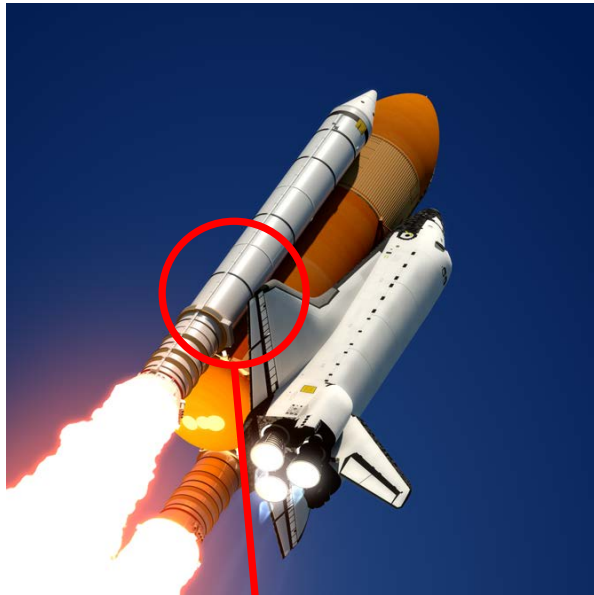


First shuttle flight, Columbia, in April 1981
Photo: nasaspaceflight.com



Columbia burnt up in 2003, killing all 7 crew members
Photo: cbsnews.com

2) Challenger



Challenger disintegrated in January 1986
killing all 7 crew members

Photo: no.wikipedia.org

An inherently dangerous machine with a accident record equivalent to over 270 fatal US airline accidents a day. No one would fly with that risk.

Opponents of animal research would claim similar unreliability for animal experiments...

Details are important!!

Planning is important!



- Complex machines (animals) create *known or unknown unknowns* (interactions between parts that are impossible to foresee until you “fly”)
- Basic design weaknesses (susceptibility to low temperatures and damage from ice and foam), *which the engineers knew about!*
- Pressure to launch (political, media). Publish or perish.
- Bad management decisions (pushing the safety envelope):
 - “We’ve got away with it before”
 - “We’ve managed to publish the experiments before”
- Often a combination of many factors, each of which may be harmless until they occur simultaneously
 - That is not a reason to ignore “insignificant” issues!
 - Attention to detail

But why do we need PREPARE when we have ARRIVE?

The ARRIVE guidelines '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>

Some examples...



The Lonely Mouse

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

Increased hypothermia in response to treatment with a serotonergic agonist

<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

Ian Johnston Science Correspondent | [@montaukian](#) | Tuesday 21 March 2017 10:58 GMT | [3 comments](#)



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

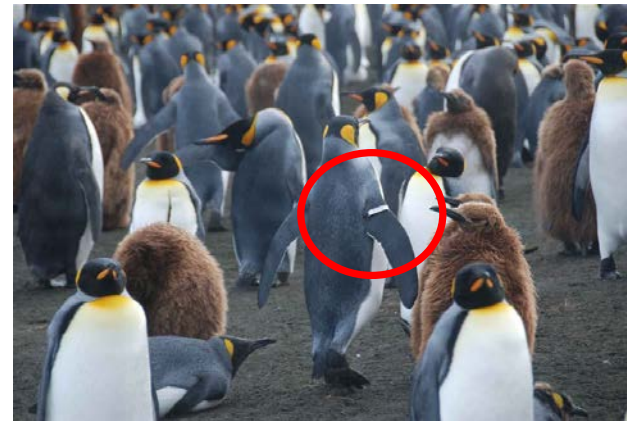
Increased hypothermia in response to treatment with a serotonergic agonist

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

”Simple” identification methods?



Photo: T. Poppe, NMBU



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

Identification methods are not always 'simple'



photo: Svalbardposten



SMERTER: Denne villreinen måtte avlives i Nordfjella. En isklump på GPS halsbåndet hadde vokst seg større enn hodet på reinen.

Av TOR-HARTVIG BONDØ og LINN K. YTTERVIK
(VG) 22.01.2016 20:27

49

photo: vg.no

"Simple" techniques?



Photo: NMBU

Are they even feasible?

*For example, intramuscular injections
in mice*

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.

'x 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?'

PREPARE:

Planning Research Involving Experimental Procedures on Animals: Recommendations for Excellence

PREPARE recommends attention to the following:

Preparation

1. Literature searches
2. Legal issues
3. Ethical issues, Harm-Benefit Assessment and humane endpoints
4. Experimental design and statistical analysis

Dialogue with 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

Not part of the ARRIVE checklist

Methods

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

The PREPARE Guidelines Checklist

Planning Research Involving Experimental Procedures on Animals: Recommendations for Excellence

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

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PREPARE¹ consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE².

PREPARE covers the three broad areas which determine the quality of the preparation for animal studies:

1. Formulation of the study
2. Dialogue between scientists and animal research experts
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 | <input type="checkbox"/> Consider the use of systematic reviews. <input type="checkbox"/> Decide upon databases and information specialists to be consulted, and construct search terms. <input type="checkbox"/> Assess the relevance of the species to be used, its biology and welfare needs. <input type="checkbox"/> Assess the reproducibility and translatability of the project. |
| 2. Legal issues | <input type="checkbox"/> Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. <input type="checkbox"/> Locate relevant guidance documents (e.g. EU guidance on project evaluation). |
| 3. Ethical issues, Harm-Benefit Analysis and humane endpoints | <input type="checkbox"/> Construct a lay summary. <input type="checkbox"/> In dialogue with local ethics committees, consider whether statements about this type of research have already been produced. <input type="checkbox"/> Address the 3Rs (Replacement, Reduction, Refinement) and the 3Ss (Good Science, Good Sense, Good Sensibilities). <input type="checkbox"/> Consider pre-registration and the publication of negative results. <input type="checkbox"/> Perform a Harm-Benefit Assessment and justify any likely animal harm. <input type="checkbox"/> Discuss the learning objectives, if the animal use is for educational or training purposes. <input type="checkbox"/> Allocate a severity classification to the project. <input type="checkbox"/> Define objective, easily measurable and unequivocal humane endpoints. <input type="checkbox"/> Discuss the justification, if any, for death as an end-point. |
| 4. Experimental design and statistical analysis | <input type="checkbox"/> Form a clear hypothesis, with primary and secondary outcomes. <input type="checkbox"/> Consider pilot studies, power and significance levels, the experimental unit, animal numbers, randomisation, avoidance of observer bias, and inclusion and exclusion criteria. |

| Topic | Recommendation |
|--|---|
| (B) Dialogue between scientists and animal research experts | |
| 5. Objectives and timescale, funding and division of labour | <input type="checkbox"/> Arrange meetings with all relevant staff when early plans for the project exist. <input type="checkbox"/> Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. <input type="checkbox"/> Discuss and disclose all expected and potential costs. <input type="checkbox"/> Construct a detailed plan for division of labour and expenses at all stages of the study. |
| 6. Facility evaluation | <input type="checkbox"/> Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. <input type="checkbox"/> Discuss staffing levels at times of extra risk. |
| 7. Education and training | <input type="checkbox"/> Assess the current competence of staff members and the need for further education or training prior to the study. |
| 8. Health risks, waste disposal and decontamination | <input type="checkbox"/> Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. <input type="checkbox"/> Assess, and if necessary produce, specific guidance for all stages of the project. <input type="checkbox"/> 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 | <input type="checkbox"/> Provide as much information as possible about test substances. <input type="checkbox"/> Consider the feasibility and validity of test procedures and the skills needed to perform them. |
| 10. Experimental animals | <input type="checkbox"/> Consider the suitability of the animal species to answer the experimental questions with the least suffering. <input type="checkbox"/> Decide upon the characteristics of the animals that are essential for the study and for reporting. <input type="checkbox"/> Avoid generation of surplus animals. |
| 11. Quarantine and health monitoring | <input type="checkbox"/> Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel. |
| 12. Housing and husbandry | <input type="checkbox"/> Attend to the animals' specific instincts and needs, in collaboration with expert staff. <input type="checkbox"/> Discuss acclimation, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing). |
| 13. Experimental procedures | <input type="checkbox"/> Develop refined procedures for capture, immobilisation, marking, and release or re-homing. <input type="checkbox"/> Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques. |
| 14. Humane killing, release, re-use or re-homing | <input type="checkbox"/> Consult relevant legislation and guidelines well in advance of the study. <input type="checkbox"/> Define primary and emergency methods for humane killing. <input type="checkbox"/> Assess the competence of those who may have to perform these tasks. |
| 15. Necropsy | <input type="checkbox"/> Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples. |

To be translated into several languages

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

norecopa.no/PREPARE



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



NORSK ENGLISH

Search:

About Norecopa | Alternatives | Databases & Guidelines | Education & training | Legislation | Meetings | More resources | News | PREPARE | Species

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

norecopa.no / PREPAREtext / 2-Ethical issues, Harm-Benefit Analysis and humane endpoints



Harm-Benefit Analysis

Harm-Benefit analysis, 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](#). Specific justification of all unalleviated animal suffering must be provided. Detailed guidance on how to conduct a harm-benefit analysis is available in [a working group report from AALAS/FELASA](#) and in [a collection of documents available at the RSPCA website](#).

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

Contract between the animal facility and the research group

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

Evaluation of the facility

- suitability for the experiment
- competence of the staff
- availability of sufficient equipment
- availability of sufficient staff

Checklists like the AAALAC accreditation Program Description template may be helpful here.

| | Animal facility | Researcher | Not applicable |
|---|-----------------|------------|----------------|
| <i>Animal:</i> | | | |
| 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) | | | |
| <i>Environment:</i> | | | |
| 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 | | | |
| <i>Housing:</i> | | | |
| Free-range, shelf, cabinet, isolator | | | |
| Cage type and size | | | |
| Number and method of distribution of animals per cage | | | |

AAALAC accreditation Program Description template

<https://www.aaalac.org/programdesc/index.cfm>

Covers

1. The animal care and use programme
2. Animal environment, housing and management
3. Veterinary care
4. Physical plant

68-page Word document with sub-headings under these four main points

PREPARE is **not just a checklist**, published once and for all.

The PREPARE website will form a dynamic set of recommendations which will evolve and contain more links as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

PREPARE is not prescriptive and is not meant to suffocate creativity, it are designed to help eliminate the artefacts caused by factors which have nothing to do with the treatment itself.

The PREPARE guidelines and website are currently under peer review in the journal *Laboratory Animals* and will be published under Open Access.



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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- Novo Nordisk
- Scottish Accreditation Board
- Stiansen Foundation
- US Department of Agriculture, Animal Welfare Information Center

