What are COST (European Cooperation in Science and Technology) Actions?

www.cost.eu

Visual identity of COST (logo):

A COST (European Cooperation in Science and Technology) is a funding organisation for research and innovation networks.

COST (European Cooperation in Science and Technology) is a pan-European intergovernmental framework with over 50 years of experience in creating open networks of excellence, COST Actions, in all scientific fields, where knowledge is freely shared among all types of specialists using bottom up principles.

COST nourishes open, free spaces where people and ideas can grow. This helps internationalisation of scientific research and communities and leads to true breakthroughs in science and technology in Europe and beyond.

COST Actions are:

Pan-European and globally connected: the COST inter-governmental framework spans 41 Full

Members, one Cooperating Member and one Partner Member; Third States/International Partner

Countries (IPCs), Near Neighbour Countries (NNCs) and Specific Organisations may join Actions as

well;

Bottom-up: COST welcomes any novel, original and innovative idea, i.e. there are no pre-defined topics / targets;

Open: COST Actions can grow in size during their lifetime, all stakeholders and new participants can join;

Unique: as a platform to coordinate national research funding and resources within a well-defined framework;

Interdisciplinary: COST Actions bridge different research communities, disciplines, fields and methodologies;

Outcome and Impact-Oriented: COST Actions are monitored for their expected output and impact.

Oriented: COST Actions are monitored for their expected output and impact.

COST Actions are set up to achieve specific objectives within their **four-year duration**, based upon the sharing, creation, dissemination and application of knowledge.

The average yearly budget allocated to COST Actions is estimated at **EUR 150 000.**

The budget of each Action depends on the size of the Network, on the implementation of the Openness and Inclusiveness principle, and on the budget available to the COST Association.

The COST Actions' objectives are achieved through the COST networking tools:

Examples of COST Action networking activities

Meetings (i.e. Management Committee Meetings, Working Group Meetings, Workshops, Conferences);

Training Schools,

Mobility of Researchers and Innovators (Short-Term Scientific Missions (STSMs) and Virtual Mobility;

Presentation at conferences organised by third parties (ITC Conference presentations and Dissemination presentations)

Further, COST Actions can receive funding for other expenses supporting the COST Action:

What is COST Action IMPROVE (CA21139)?

Project website: www.cost.eu/actions/CA21139/

CA21139 - 3Rs concepts to improve the quality of biomedical science (IMPROVE)

Start date: 21/10/2022

End date: 20/10/2026

CA IMPROVE logo (under development):

Who is participating?

CA IMPROVE brings together experts form more than 30 + EU and non-EU countries.

Croatia is so far represented by (CA IMPROVE web page accessed on April 23. 2023)**:**

1) Ivana Vrhovac Madunic (Institute of Medical Research and Occupational Health, Zagreb), Management Committee-MC member, Working Groups-WGs 1&4 member (see below)

2) Dasa Seveljevic-Jaran (representing CroLASA, employed at Selvita Ltd, Zagreb), MC member and WGs 1&2 member and

3) Zvonimir Koporc (Catholic University of Croatia) as WGs 1-4 member.

How to participate in an existing Action?

COST Actions are different to many other EU funded projects because **it is possible to join and participate in a research network even once it has started running**, this feature applies throughout the entire lifespan of the Action. This is the openness of COST.

How can you participate?

Express your interest to join any of the working groups by applying on the CA IMPROVE website.

***NOTA BENE*:**

It is required to have an e-COST profile to submit your application. If needed, create it first and then apply to participate in CA IMPROVE working groups of interest.

Before you proceed with the application, inform yourself and take time to:

1) Read the Project Description (Memorandum of Understanding-MoU)

2) Inform the Main Proposer (Chair of your interest (by e-mail)

Winfried Neuhaus (Austria), Action Chair, e-mail: winfried.neuhaus@ait.ac.at

3) Apply to join the **Working Groups-WG** of interest (and respective subgroups, not listed here):

WG 1) Quality and translatability of science (Leader: Ioanna Sandvig, Norway)

WG 2) Implementation (Leader: Doris Wilflingseder, Austria)

WG 3) Dissemination (Leader: Almir Badnjevic, BiH)

WG 4) Education (Leader: Anna Olsson, Portugal)

The main aim of the COST Action IMPROVE:

The main aim is to establish a network which will work to refine, harmonise and promote 3Rs concepts, data and documents and will encourage their implementation in preclinical research practices, aiming to improve the quality and overall translatability of preclinical research and biomedical science.

Figure 1: Main topics of the COST Action IMPROVE

Description of the CA IMPROVE:

Awareness of the existence of a reproducibility and predictability crisis in biomedical science has increased over the last decade.

The reproducibility crisis addresses the translational failure of preclinical research due to which many promising drugs tested in animal models fail to show similar effects in human trials. The translational failure is due to the limited validity of various animal models, the inadequate design practices,

inadequate conduct and statistical methodology as well as inadequate reporting/publication practices.

There have been many publications reviewing why preclinical research is irreproducible and lacking predictability. Better statistical methodology will play a central role in improving the reproducibility of science to produce robust and reproducible research. Another area of improvement is the development of novel, higher validity models, providing more methodological detail on use of pharmacologic and non-pharmacologic refinements, thus contributing to overall research translatability and predictability.

With overall translatability improvements in mind, the development and introduction of new, powerful concepts for biomedical research is essential to reduce the production of non-reproducible and non-predictive data. This has immense scientific, economic and social significance.

In this context, COST action IMPROVE proposes that the findings and concepts from the 3Rs field can greatly help improve the biomedical research on several levels.

What are the variables/factors impacting the preclinical research outcomes?

Confounding factors influence both the dependent and independent variables; they continue to be identified, suggesting that our knowledge of their existence is far from complete.

The husbandry and laboratory environmental factors i.e. experimental protocol/test related factors vary between the experiments and laboratories, and more importantly, these external factors hold the potential to intefere with the research outputs.

In general, the quality of research results is influenced by the frequency and severity of interventions inflicted on the model animal and the number of refinements implemented to counteract the harms stemming from them.

The quality assurance of preclinical research relies on good veterinary, laboratory and research practices aiming to protect the welfare of research animals. The methodological inadeqacies plaguing the preclinical research have become the main drivers of the paradigm shift that seeks to treat the animals in preclinical studies not as instruments but as patients in clinical studies.

How are variables controlled in preclinical research?

By complying with **PREPARE good practices guidelines** (addressing preparation and experimental design aspects) and **ARRIVE guidelines** (addressing conduct and reporting practices of preclinical research, **Appendix 1 & 2**) as well as the disease-specific guidelines, we control variation and thus support the overall translatability of preclinical research.

External factors/variables:

Husbandry-related variables:

Husbandry-related variables are determined by the biosecurity measures guarding the welfare of laboratory animals, such as the macroenvironmental conditions (% rH,°C, lux, dB) maintained in the secondary enclosure (the holding room), compliant with bio-exlusion and bio-inclusion practices. Inside the primary enclosure (the cage), laboratory animals are group housed on solid bedded cage floor additionaly structured with various environmental enrichment-EE items (examples of non-

pharmacologic refinements) allowing captive animals come control over their living environment (the microenvironment). Addition of EE into the cage prevents boredom, frustration and stress (sterotypies) by motivating animals to interact with inserts and the cage-mates (the most important refinement of all) and to engage in species-specific behaviour (tunneling, climbing, exploring, nesting, huddling, gnawing etc).

In order to maintain desired microbiological quality of research animals, the cage inserts (including water and bedding quality) should be of controlled and standardised quality (chemically and biologically inert, ideally confirmed by Certificates of Analysis-CoA). The animals are kept in a variety of cage designs, open top cages, filter top cages or IVC cages, each to be used depending on the targeted level of biosecurity practices to be implemented and maintained.

Animals relate to their physical environment (the micro and macro-environment) *via* auditory, visual, olfactory, gustatory and tactile cues, the stimuli coming from inside the cage as well as from the holding room and its structures.

Animals are additionally stressed by the cage changing frequency and by the routine care takers' handling. The time of the day (as well as the season) when husbandry or experiment related practices are conducted are also known external variables and should be clearly defined and reported.

Test/experimental protocol related variables:

The biggest stress (and pain) come from specific experimental protocol methodology; research animals participating in an experiment are subjected to different scientific methods of varying frequency and cummulative severity which depends on the testing agents and reagents used *in vivo,* as well as the disease phenotype to be modelled or the genotype (transgenic animal modelling disease) of the animal under study.

Internal factors/variables:

Pain treatment is an ethical and scientific imperative; the pain treatment should not negatively affect the translational properties of the model (e.g. immune-related parameters). In comparison, the impact of analgesia is more predictable than the effects of the pain left untreated.

Pain left untreated holds the potential to impact the animal and in turn, the research ouputs.

Other internal factors such as species, age, sex, strain (genotype), social and health status of animal/s under study may also impact the results as may the interactions of these factors with the external factors.

Categories of experimental biases:

Experimental biases stem from failure to clearly document the practical applications of refinements (pharmacologic and non-pharmacologic) in preclinical research and they prevent scientists from correctly attributing an observed effect to a treatment or intervention under investigation.

Animal experiments more closely represent controlled trials: the efficacy study ideally aims to measure an effect of an intervention/treatment by observing the effects in same animals at the same time, thus controlling variation. This paradigm is currently being challenged as yet another possible cause of

translational failure and the term coined for it is “standardisation fallacy” but this subject will be addressed elsewhere.

Ideally, research animals are strain, sex, age, weight and health/disease status matched/standardised so that the observed difference is ideally attributed to the treatment rather than a confounder.

A confounder is a factor that affects the outcome independent of the treatment used, introducing systemic errors.

There are different categories of biases affecting the preclinical research.

At the phase of study design, practices of minimising (controlling) them should be implemented:

- **selection bias** can be minimised by using randomisation and by including both sexes of animals in research, thus avoiding sex bias as biological variable
- **detection bias** can be minimised by using blinding of outcome assessments, thus minimising the effect of assessors' expectations and subjectivity on results' assessment
- **attrition bias** can be minimised by clearly defining inclusion and exclusion criteria (including humane end points-HEPs) by stating the number of animals assigned to an experimental protocol (per group) and the number of drop-outs (i.e. the number of animals excluded from the experiment before the defined experiment termination)
- **publication bias** can be minimised by publishing both negtive and positive results and, equally important, by chosing the adequate statistical analysis and reporting it in sufficient detail

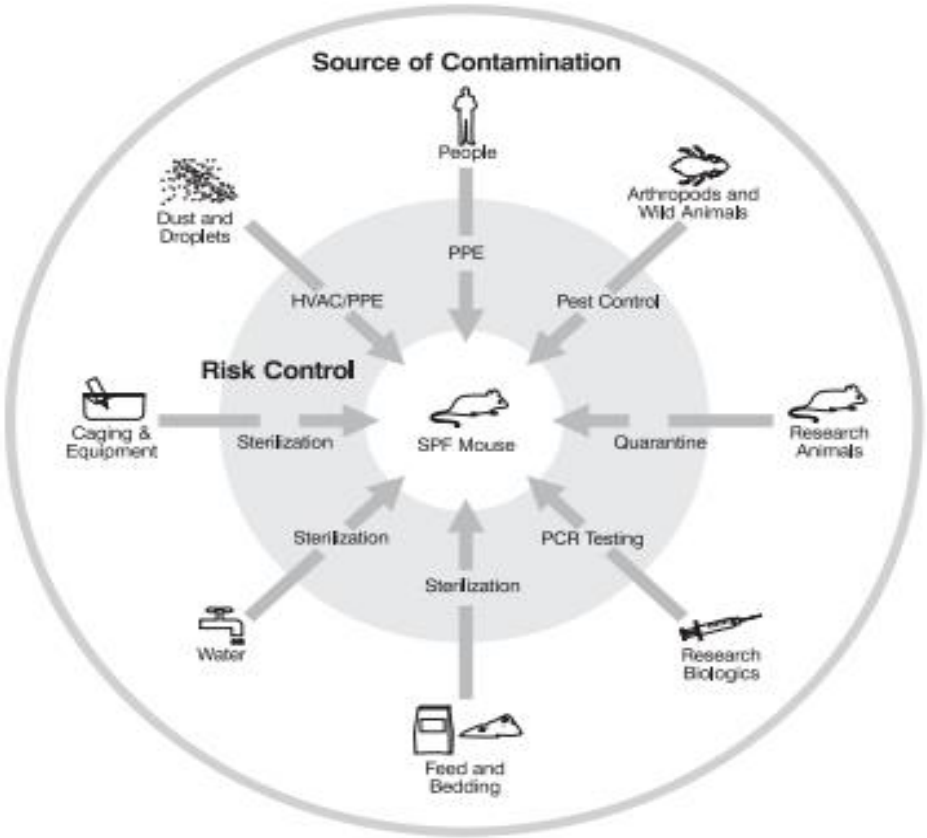
- **imprecision** (introducing random error)

Husbandry and test related variables:

A Guide to Modern Strategies for Infection Surveillance of Rodent Populations

Basic Biosecurity Considerations

2022 Charles River International Inc. publication



Variables affecting the results from preclinical pain research:

Jeffrey S Mogil.

Laboratory environmental factors and pain behavior:

the relevance of unknown unknowns to reproducibility and translation.

Volume 46, No. 4, *Lab Animal* , 2017.

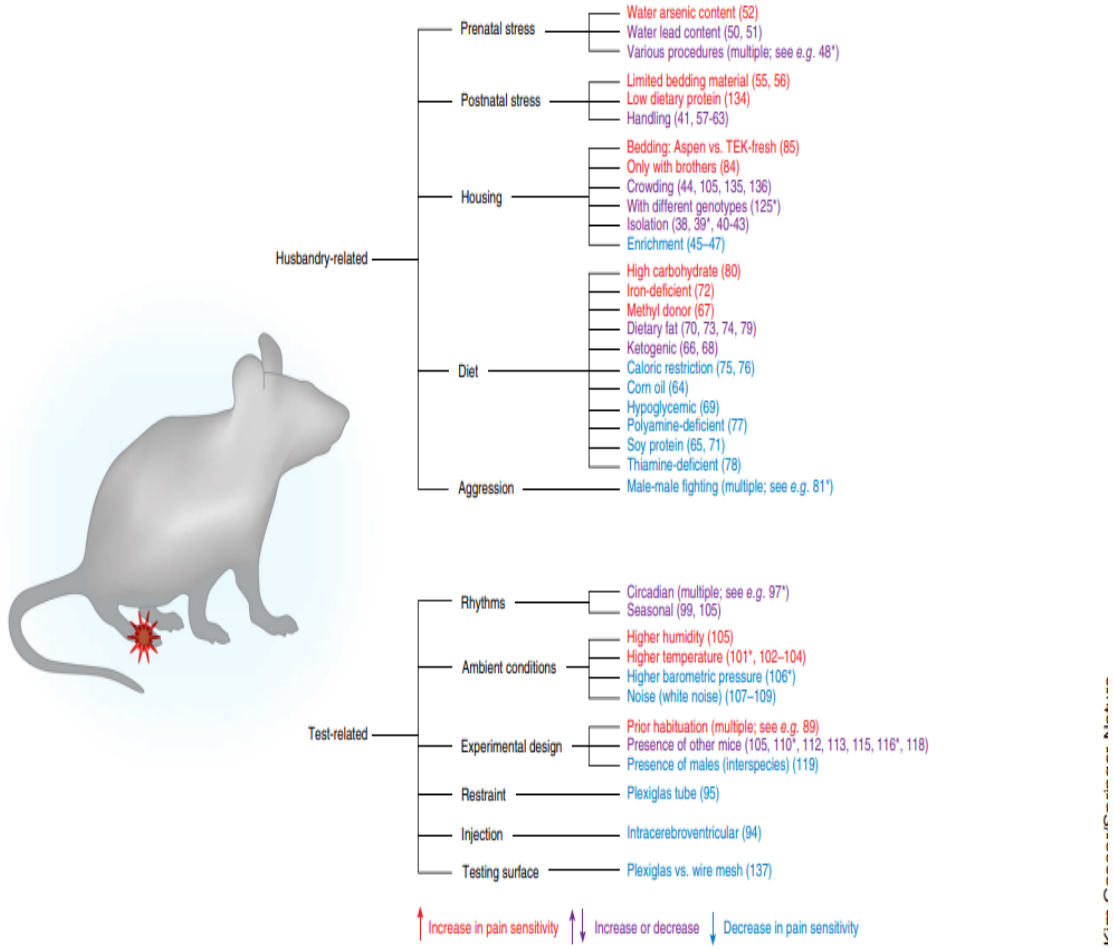


FIGURE 1 | Factors significantly affecting pain sensitivity in rodent models and sample references. Only factors that might credibly vary between laboratories are considered. For the factor "Diet", we excluded diabetes, hypertension and obesity models. We also excluded experimental stressors or procedures such as shock, restraint, prolonged maternal separation, or sucrose feeding. Only papers reporting statistically significant effects in either direction are listed. In the case of multiple papers by the same laboratory (indicated by *), only the first to be published is listed.

CA IMPROVE first steps:

1. Collect guidance documents

2. Conduct survey(s) – awareness about non-animal models; thresholds in adopting them

3. Meta research – invertebrates

4. Availability of tools

5. Determine topic(s) for first white paper(s)

6. Compile list of relevant abbreviations, including databases (both for internal communication and external use)

Recommended reading:

Winfried Neuhaus (first author) publications

- The Current Status and Work of Three Rs Centres and Platforms in Europe. *Alternatives to laboratory animals* 50 (6):381-413, 2022. DOI: 10.1177/02611929221140909
- The Rise of Three Rs centers and Platforms in Europe. *Alternatives to laboratory animals* 50 (2): 2022. DOI: 10.1177/02611929221099165
- Consensus Statement from the European Network of 3R Centres (EU3Rnet). *ALTEX* 2020. DOI: 10.14573/altex.2010061

More on COST Action:

You can learn more about COST Action rules by reading the following documents, all of which are avialable at www.cost.eu web site:

- Rules for participation in and implementation of COST activities
- Action proposal submission, evaluation, selection and approval (SESA)
- Action management, monitoring and final assessment
- Annotated Rules for COST Actions
- Guidelines for Action management, monitoring and assessment
- Guidelines for the communication, dissemination and exploitation of COST Action results and outcomes
- Rules and principles for COST Activities
- COST Code of Conduct

How to propose your own Action?

If you would like to propose your own COST Action research network, you must do so through the COST Open Call.

Prepared by:

Dasa Seveljevic-Jaran

(CroLASA Bilten 2022)

Appendix 1: **PREPARE** guideline checklist (English and Croatian version)

Appendix 2: **ARRIVE** guideline checklist

Appendix 3: **Biotech-Xchange**.com (NL) 3R platform flyer

PREPARE

The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

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

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PREPARE[1] consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE[2].
PREPARE covers the three broad areas which determine the quality of the preparation for animal studies:

1. **Formulation of the study**
2. **Dialogue between scientists and the animal facility**
3. **Quality control of the components in the study**

The topics will not always be addressed in the order in which they are presented here, and some topics overlap. The PREPARE checklist can be adapted to meet special needs, such as field studies. PREPARE includes guidance on the management of animal facilities, since in-house experiments are dependent upon their quality. The full version of the guidelines is available on the Norecopa website, with links to global resources, at **https://norecopa.no/PREPARE**.
The PREPARE guidelines are a dynamic set which will evolve as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

Topic	Recommendation
(A) Formulation of the study	
1. Literature searches	☐ Form a clear hypothesis, with primary and secondary outcomes. ☐ Consider the use of systematic reviews. ☐ Decide upon databases and information specialists to be consulted, and construct search terms. ☐ Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and its welfare needs. ☐ Assess the reproducibility and translatability of the project.
2. Legal issues	☐ Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. ☐ Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	☐ Construct a lay summary. ☐ In dialogue with ethics committees, consider whether statements about this type of research have already been produced. ☐ Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). ☐ Consider pre-registration and the publication of negative results. ☐ Perform a harm-benefit assessment and justify any likely animal harm. ☐ Discuss the learning objectives, if the animal use is for educational or training purposes. ☐ Allocate a severity classification to the project. ☐ Define objective, easily measurable and unequivocal humane endpoints. ☐ Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	☐ Consider pilot studies, statistical power and significance levels. ☐ Define the experimental unit and decide upon animal numbers. ☐ Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.

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 preparation, 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 prior 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

1. Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattelid T (2018) PREPARE Guidelines for Planning Animal Research and Testing. Laboratory Animals, 52(2):135-141. *https://doi.org/10.1177/0023677217724823*
2. Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M et al. (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol 18(7): e3000410. *https://doi.org/10.1371/journal.pbio.3000410*

Further information

https://norecopa.no/PREPARE / *post@norecopa.no* / *@norecopa*

Kontrolna Lista PREPARE Smjernica

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

(Pripreme za provedbu istraživanja na laboratorijskim životinjama u znanstvene svrhe: preporuke za izvrsnost)

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, Oslo, Norway; [b]Royal (Dick) School of Veterinary Studies, Midlothian, U.K.; [c]Research Animals Department, Science Group, RSPCA, West Sussex, U.K.; [d]Section of Experimental Biomedicine, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Oslo, Norway; [e]Division for Research Management and External Funding, Western Norway University of Applied Sciences, 5020 Bergen, Norway.

PREPARE[1] se sastoji od smjernica za pripremu i provedbu istraživanja na životinjama koje su komplementarne sa ARRIVE[2] smjernicama za izvještavanje rezultata istraživanja na životinjama.
PREPARE kontrolna lista pokriva tri šira područja koja osiguravaju kvalitetu pripreme i provedbe istraživanja na laboratorijskim životinjama (*in-vivo* istraživanje/projekt dalje u tekstu):

1. **Opis (svrha i sadržaj) znanstvene studije**
2. **Komunikacija između znanstvenika (voditelja projekta, korisnika nastambe) i osoblja koje upravlja nastambom za laboratorijske životinje**
3. **Kontrola kvalitete svih komponenti *in-vivo* istraživanja**

Kod priprema studije ne treba se striktno držati navedenog redosljeda budući se područja preklapaju.

PREPARE kontrolna lista može se po potrebi prilagoditi i specijalnim oblicima istraživanja kao na primjer onima u okviru terenskih studija. PREPARE sadrži i smjernice upravljanja nastambom za laboratorijske životinje budući dobre prakse gospodarenja životinjama utječu na kvalitetu *in-vivo* istraživanja koja se u nastambi provode. Cjelovita verzija smjernica te brojne poveznice na srodne globalne sadržaje dostupne su na Norecopa mrežnoj stranici **https://norecopa.no/PREPARE.**

PREPARE kontrolna lista dinamični je dokument koji će se nadopunjavati budućim smjernicama koje generalno proizlaze iz najnovijih znanstvenih spoznaja u području znanosti o laboratorijskim životinjama.

Područje	Preporuke
A) Opis studije	
1. Pregled literature	• Iznesite jasnu hipotezu sa primarnim i sekundarnim ishodima studije. • Razmislite o provedbi sistematičnog pregleda literature. • Napravite izbor ključnih stručnjaka i baza podataka koje će te u postupku priprema konzultirati te ključne riječi za pretraživanje "on-line" literature. • Ocijenite prikladnost odabrane životinjske vrste i njenih bioloških svojstava ciljevima istraživanja, planirajući mjere zaštite dobrobiti životinja i smanjenje boli i nelagode kad i gdje je to moguće. • Ocijenite reproducibilnost projekta i njegov translacijski potencijal.
2. Usklađenost projekta sa zakonskim odredbama	• Ocijenite usklađenost projekta sa zakonima za korištenje životinja u znanstvene svrhe i sa zakonima koji uređuju druga područja kao na primjer transport životinja, zaštita radnika na radnom mjestu i slično. • Proučite europske zakonske odredbe i relevantne smjernice dobrih praksi i s tim u vezi pravovremeno zatražite projektnu autorizaciju te etičku evaluaciju projekta.
3. Etičke stavke, analiza šteta i koristi i definiranje humanih ishoda studije (engl. HEP)	• Napišite netehnički sažetak studije. • U komunikaciji sa institucijskim etičkim povjerenstvom provjerite da li je slični istraživački projekt u prošlosti bio predmet etičke procjene. • Sa životinjama postupajte u skladu sa 3R načelima (načela zamjene, smanjenja i poboljšanja) te 3S načelima ("good science, good sense, good sensibilities" – načela dobre znanstvene prakse, zdravog razuma i suosjećanja sa životinjama). • Razmislite o predbilježbi *in-vivo* istraživanja te objavi negativnih rezultata. • Provedite detaljnu analizu šteta i koristi te obrazložite moguće štete.

	• Diskutirajte o ishodima učenja ako se životinje koriste u svrhu educiranja novih stručnjaka. • Procijenite težinu (kumulativnu bolnost) *in-vivo* postupaka u projektu. • Definirajte objektivne, jednostavno mjerljive, humane i nedvosmislene krajnje točke kao i ranije ishode projekta (engl. Humane End Points_HEP). • Opravdajte smrtni ishod ako je on očekivani ishod projekta.
4. Dizajn pokusa i statističke analize	• Provedite pilot studije, izračun ciljane snage studije i stupnja statističke značajnosti. • Definirajte eksperimentalnu jedinicu i broj životinja sudionica pokusa. • Izaberite metodu randomizacije, spriječite pristranost promatrača i jasno definirajte klinički relevantne kriterije uključivanja i isključivanja sudionica pokusa.
B) Komunikacija između znanstvenika (korisnika nastambe) i osoblja nastambe	
5. Ciljevi, trajanje i financiranje studije; raspodjela radnih zaduženja (vođenje projekta)	• Organizirajte sastanke sa svim sudionicima istraživačkog projekta na samom početku izrade projekta. • Definirajte okvirno trajanje projekta te potrebne resurse za provedbu priprema, skrbi o životinjama, provedbu *in-vivo* procedura te procedura zbrinjavanja otpada i provođenja dekontaminacije. • Definirajte i transparentno priopćite svim sudionicima očekivane troškove provedbe projekta. • Razradite detaljni plan raspodjele radnih zaduženja za sve faze projekta.
6. Evaluacija nastambe za laboratorijske životinje	• Procijenite prikladnost raspoložive opreme i standardnih operativnih procedura u nastambi za laboratorijske životinje potrebama i ciljevima projekta te definirajte potrebe za dodatnom opremom i novim procedurama. • Definirajte najrizičnije faze projekta za čiju će uspješnu provedbu trebati osigurati dodatno znanstveno i tehničko osoblje.
7. Edukacija i osposobljavanje osoblja	• Procijenite trenutačni nivo kompetencija osoblja i identificrajte one koje treba dodatno educirati u specifičnom području i osposobiti prije provođenja studije.
8. Zdravstveni rizici, postupci zbrinjavanja otpada i dekontaminacije	• Izvršite procjenu rizika u suradnji sa osobljem nastambe, za sve direktne i indirektne sudionike projekta i laboratorijske životinje. • Utvrdite postojanje relevantnih smjernica dobrih praksi i po potrebi izradite specifične smjernice za svaku fazu projekta. • Definirajte načine dekontaminacije odnosno neškodljivog zbrinjavanja svih kategorija otpada koji se generira u vrijeme provedbe projekta.
C) Kontrola kvalitete svih komponenti *in-vivo* istraživanja	
9. Testne tvari i procedure	• Osigurajte maksimalnu količinu informacija o testnim tvarima i rizicima prilikom njihovog rukovanja i primjene *in-vivo.* • Razmislite o izvedivosti i valjanosti pokusnih procedura te potrebnim kompetencijama (na pr. sigurno rukovanje opasnim kemikalijama) projektnog osoblja.
10. Pokusne životinje	• Definirajte osnovne karakteristike životinja koje udovoljavaju ciljevima istraživanja i standarde izvještavanja rezultata *in-vivo* istraživanja. • Koristite najmanji mogući broj životinja koji neće ugroziti statističku snagu studije.
11. Karantena i zdravstveni nadzor	• Definirajte željeni zdravstveni (mikrobiološki i genetski) status životinja, eventualne potrebe za njihovim prijevozom i provedbom bio-sigurnosnih mjera nakon njihove dostave u nastambu te za vrijeme provedbe pokusa kao i načine zdravstvenog nadzora životinja i potencijalnih zdravstvenih rizika za osoblje.
12. Uvjeti držanja i gospodarenje životinjama	• Uzmite u obzir za životinjsku vrstu specifična instinktivna i svrsishodna ponašanja i u suradnji sa stručnim osobljem definirajte optimalne uvjete držanja i dodatke kavezu. • Odredite trajanje aklimatizacije ili karantene, optimalne uvjete skrbi, mikroklimatske uvjete te sve limitirajuće okolnosti određene *in-vivo* protokolom (npr. trajanje i frekvenciju prisilnog gladovanja životinja, pojedinačni smještaj životinja i slično).
13. Eksperimentalne procedure	• Razradite opcije poboljšanja stresnih procedura označavanja, rukovanja, obuzdavanja, i nakon završetka pokusa, prilikom eventualnog vraćanja životinja na slobodu ili njihovog smještaja kod udomitelja. • Razradite opcije poboljšanja bolnih procedura prilikom primjene testnih tvari, uzorkovanja tkiva, analgezije i anestezije, kirurških zahvata i drugih sličnih praksi.

14. Eutanazija, ponovno korištenje životinja u projektima, vraćanje životinja na slobodu i udomljavanje	• Konzultirajte relevantne zakonske odredbe i važeće smjernice dobrih praksi na vrijeme, prije provedbe projekta. • Definirajte glavne i zamjenske metode humane eutanazije. • Procijenite kompetencije osoblja zaduženog za eutanaziju životinja iz projekta.
15. Razudba (*post mortem* procedure)	• Izradite detaljni protokol sa svim fazama razudbe, osigurajte sljedivost svih preuzetih uzoraka odnosno identifikatore svih životinja, životinjskih uzoraka i podataka proizišlih iz *in-vivo* istraživanja te definirajte njihove lokacije i prikladne uvjete skladištenja i eventualnog transporta.

Literatura:

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.

NOTE: Please save this file locally before filling in the table, DO NOT work on the file within your internet browser as changes will not be saved. Adobe Acrobat Reader (available free here) is recommended for completion.

The ARRIVE guidelines 2.0: author checklist

The ARRIVE Essential 10

These items are the basic minimum to include in a manuscript. Without this information, readers and reviewers cannot assess the reliability of the findings.

Item		Recommendation	Section/line number, or reason for not reporting
Study design	1	For each experiment, provide brief details of study design including: a. The groups being compared, including control groups. If no control group has been used, the rationale should be stated. b. The experimental unit (e.g. a single animal, litter, or cage of animals).	
Sample size	2	a. Specify the exact number of experimental units allocated to each group, and the total number in each experiment. Also indicate the total number of animals used. b. Explain how the sample size was decided. Provide details of any *a priori* sample size calculation, if done.	
Inclusion and exclusion criteria	3	a. Describe any criteria used for including and excluding animals (or experimental units) during the experiment, and data points during the analysis. Specify if these criteria were established *a priori.* If no criteria were set, state this explicitly. b. For each experimental group, report any animals, experimental units or data points not included in the analysis and explain why. If there were no exclusions, state so. c. For each analysis, report the exact value of *n* in each experimental group.	
Randomisation	4	a. State whether randomisation was used to allocate experimental units to control and treatment groups. If done, provide the method used to generate the randomisation sequence. b. Describe the strategy used to minimise potential confounders such as the order of treatments and measurements, or animal/cage location. If confounders were not controlled, state this explicitly.	
Blinding	5	Describe who was aware of the group allocation at the different stages of the experiment (during the allocation, the conduct of the experiment, the outcome assessment, and the data analysis).	
Outcome measures	6	a. Clearly define all outcome measures assessed (e.g. cell death, molecular markers, or behavioural changes). b. For hypothesis-testing studies, specify the primary outcome measure, i.e. the outcome measure that was used to determine the sample size.	
Statistical methods	7	a. Provide details of the statistical methods used for each analysis, including software used. b. Describe any methods used to assess whether the data met the assumptions of the statistical approach, and what was done if the assumptions were not met.	
Experimental animals	8	a. Provide species-appropriate details of the animals used, including species, strain and substrain, sex, age or developmental stage, and, if relevant, weight. b. Provide further relevant information on the provenance of animals, health/immune status, genetic modification status, genotype, and any previous procedures.	
Experimental procedures	9	For each experimental group, including controls, describe the procedures in enough detail to allow others to replicate them, including: a. What was done, how it was done and what was used. b. When and how often. c. Where (including detail of any acclimatisation periods). d. Why (provide rationale for procedures).	
Results	10	For each experiment conducted, including independent replications, report: a. Summary/descriptive statistics for each experimental group, with a measure of variability where applicable (e.g. mean and SD, or median and range). b. If applicable, the effect size with a confidence interval.	

The Recommended Set

These items complement the Essential 10 and add important context to the study. Reporting the items in both sets represents best practice.

Item		Recommendation	Section/line number, or reason for not reporting
Abstract	11	Provide an accurate summary of the research objectives, animal species, strain and sex, key methods, principal findings, and study conclusions.	
Background	12	a. Include sufficient scientific background to understand the rationale and context for the study, and explain the experimental approach. b. Explain how the animal species and model used address the scientific objectives and, where appropriate, the relevance to human biology.	
Objectives	13	Clearly describe the research question, research objectives and, where appropriate, specific hypotheses being tested.	
Ethical statement	14	Provide the name of the ethical review committee or equivalent that has approved the use of animals in this study, and any relevant licence or protocol numbers (if applicable). If ethical approval was not sought or granted, provide a justification.	
Housing and husbandry	15	Provide details of housing and husbandry conditions, including any environmental enrichment.	
Animal care and monitoring	16	a. Describe any interventions or steps taken in the experimental protocols to reduce pain, suffering and distress. b. Report any expected or unexpected adverse events. c. Describe the humane endpoints established for the study, the signs that were monitored and the frequency of monitoring. If the study did not have humane endpoints, state this.	
Interpretation/ scientific implications	17	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including potential sources of bias, limitations of the animal model, and imprecision associated with the results.	
Generalisability/ translation	18	Comment on whether, and how, the findings of this study are likely to generalise to other species or experimental conditions, including any relevance to human biology (where appropriate).	
Protocol registration	19	Provide a statement indicating whether a protocol (including the research question, key design features, and analysis plan) was prepared before the study, and if and where this protocol was registered.	
Data access	20	Provide a statement describing if and where study data are available.	
Declaration of interests	21	a. Declare any potential conflicts of interest, including financial and non-financial. If none exist, this should be stated. b. List all funding sources (including grant identifier) and the role of the funder(s) in the design, analysis and reporting of the study.	

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