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Improving the publication standards of research involving animals

Systematic analysis has revealed that a significant proportion of publications reporting research involving animals lack information on study planning, study executionⁱ, and/or statistical analysis. This situation can potentially lead to negative consequences such as unnecessary animal experiments. A number of initiatives aimed at improving the standards of publishing research involving animal models have recently been initiated and led to several sets of guidelines for authors, reviewers and journal editors. The most commonly known guidelines are ARRIVEⁱⁱ, the GSPCⁱⁱⁱ, ILAR^{iv} and most recently ICLAS guidelines^v.

In particular, the ARRIVE guidelines (published in 2010) have been endorsed by over 300 journals worldwide^{vi}. While this represents a significant step toward the implementation of general rules for the publication of animal research, more needs to be done to arrive at universal and uniform standards for the information to be included in publications.

The following issues need discussion and/or improvement:

1. Different guidelines exist while many journals have not yet adopted any of these. The involved organisations (see above) and journals should join effort to establish a common set of guidelines and requirements concerning the reporting of design, execution and analysis of studies involving animals in publications. Such a unified set of guidelines should then be implemented by all journals. Universal standards would be the most effective measure to prevent seriously flawed studies from being published.
2. Journals should provide authors with sufficient space to describe all relevant details of research and analysis such that studies can be judged with respect to their planning, methodology, statistical verification and reproducibility of all results. The necessary space can be provided in the context of the methods section and/or supplemental online sections. In addition, authors should be requested to describe efforts to implement the 3Rs^{vii}, comment on the severity and state under which permits and in which legal framework the experiments were performed. Methods to avoid bias, such as blinding and randomization should be reported where appropriate.
3. Scientists and editors should develop a culture of vigorous and critical assessment of animal studies; the peer review system is an essential component of any control mechanism. Journals should provide reviewers with clear guidelines and every review report should contain one specific section dedicated to this evaluation. Experts in the design and analysis of animal studies must be involved in the peer review process.
4. Authors should be encouraged to publish and/or at least include a paragraph in their manuscripts describing experiments of robust design and conduct that failed to advance the working hypothesis (so-called “negative” results). This will be an effective measure

to avoid unjustified duplication by others, which in the worst case may result in unnecessary use of animals and resources.

5. Authors should make all robust primary data (published and so-called “negative” results) available in curated databases, which should be open access and searchable by keywords (see workshop 2).
6. Life-science students should be trained in best experimental practice and the ethics of animal research consistent with publication guidelines to facilitate high standards in reporting. In fact, researchers must be fully aware of the publication guidelines at the planning stage to facilitate meaningful and accurate reporting at the end of their studies.

To instigate change, international best practice guidelines governing animal studies must be endorsed by scientists, universities, research institutions, learned societies, animal welfare officers, granting agencies and journals. The implementation of best practice publication standards requires cooperation of all stakeholders.

References

ⁱ Sena et al 2007, Tins. Vesterinen et al 2010 MS. Frantzias et al 2011 Ann Neurol

ⁱⁱ <http://www.nc3rs.org.uk/ARRIVE>

ⁱⁱⁱ Gold Standard Publication Checklist: <http://www.ncbi.nlm.nih.gov/pubmed/20507187>

^{iv} <http://dels.nas.edu/ilar>

^v International Council for Laboratory Animal Science Guidelines: <http://iclas.org/committees/ethics-and-animal-welfare-committee>

^{vi} Animal Research: Reporting In Vivo Experiments: <http://www.nc3rs.org.uk/ARRIVEjournals>

^{vii} „Replace, Reduce, Refine“ – reference to Basel Declaration paper



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Open access to maximize the value of animal research

Key position statement

The scientific research community, including the public and private sector, is committed to maximising the value of data generated from animal research in order to enhance the design of future studies. This can be achieved by archiving non-competitive data derived from animal experiments in publicly accessible repositories, and by sharing protocols and data on the characteristics and optimal use of each animal model as widely as possible. This could potentially lead to the refinement of experimental protocols and the reduction of the number of animals used in research. It could also inform strategic decision-making regarding future academic and commercial research. Animal usage may also be reduced through wider use of animal repositories. Data, protocols and results from well designed and conducted research using animals should also be readily available in a curated, searchable form. Sharing research outputs will help to maximise the knowledge base resulting from research, improve research outcomes and avoid unjustified duplication of work using animals.

The scope of this commitment should extend to individual researchers, research institutions, research funders, publishers, industry and government departments, which fund and undertake research using animals.

Publishing results of animal experimentation in scientific journals:

- 1) The approved guidelines for publication¹ of research using animals including ARRIVE, ILAR, ICLAS and GSPC should be widely supported.
- 2) Additional open access publications, or on line space in existing journals, for well-designed studies that do not support the initial hypothesis, and for 'verification'/'replication' studies should be provided.
- 3) Published papers should include a clear statement on how data and materials related to the paper can be accessed.
- 4) It should be made a condition of publication that where appropriate, raw data related to the publication are deposited in a recognised database to make this standard practice. E.g. sequence data.

¹ <http://www.nc3rs.org.uk/downloaddoc.asp?id=1206&page=1357&skin=0>

- 5) Funding bodies should require details of publication plans to be included in the proposals for work. There should be a requirement for all grants using animals to publish 'something' of journal quality, irrespective of whether the initial hypotheses have been supported or not.
- 6) The research sector should create incentives for the publication of all results so that publication becomes normal practice. This could include developing a system where the number of times certain publications are accessed via a repository system is counted.
- 7) Improve research identifiers (such as ORCID²) and develop citation incentives to acknowledge researchers who publish all of their findings.

Accessibility of resources for animal studies:

- 8) Resources and repositories such as INFRAFRONTIER/EMMA (www.infrafrontier.eu) or KOMP (<https://www.komp.org>) for mice, the Zebrafish International Resource Center ZIRC (<http://zebrafish.org>) the Rat Genome Database (<http://rgd.mcw.edu>) or FlyBase (<http://flybase.org>) have established successful models for sharing animal models, protocols and genetic information, as well as a wealth of cross-referenced data. Their use should be encouraged and their sustainability secured by increased EU, other public sector and charitable funding.
- 9) Systematic approaches like INFRAFRONTIER or the IMPC use high-end technology and common standards and protocols to minimize impact on animals and maximise scientific output with the minimum amount of animals. Researchers should be encouraged to use these services.
- 10) Repositories such as INFRAFRONTIER/EMMA act as 'clearing houses' which can connect researchers working on specific disease models or drug targets, with others in the field who have used similar animal models.

Accessibility of data on animal studies:

- 11) Encourage platforms for the publication and dissemination of all well designed and conducted research findings irrespective of whether they support the initial hypotheses or not.
- 12) Develop mechanisms to increase the sharing of research resources, protocols, and data through cross-linked, open-access repositories and databases.
- 13) A future vision could encompass a central portal through which interrogation of all animal studies, published or unpublished could be accomplished.
- 14) Improve awareness of the importance of, and training in, undertaking systematic reviews of available information in the literature and in dedicated bioinformatics resources as part of the study design³ process, as well as training and method development on meta-analysis.
- 15) Encourage increased searching and use of data and existing protocols in databases such as CAMARADES⁴, eTRIKS for translational research in the remit of the IMI, FigShare⁵, Dryad⁶.

² www.orcid.org

³ Macleod, m. 'How to avoid bumping into the translational roadblock'

⁴ http://www.camarades.info/index_files/Protocols.html

⁵ <http://figshare.com/>

⁶ <http://datadryad.org/>

Issue Background

Publication of research results

- Not all research results from studies using animals are published. A recent study conducted in the Netherlands estimated that ~50% of all studies using animals in academia and only ~10% of all for profit studies are published⁷. This has a number of implications, which include:
 - Possible unjustified duplication of studies involving animals;
 - Possible premature “first in man” studies⁸;
 - Possible publication bias⁹.
- Currently, there is little incentive and very few avenues to publish so-called ‘negative’ and ‘null’ results (see workshop 1).¹⁰
- Increased sharing of experimental design and methodologies will increase the quality of future studies and maximise the knowledge gained by systematic review of previous research.
- Therefore, the following challenges with respect to open access need to be addressed:
 - A flexible enough vocabulary and data dictionary to include all robust results from animal studies in a format, which can be easily interrogated must be developed. This format must be applicable to all the various areas relying on animal experimentation.
 - It needs to be decided if in addition to *in vivo* animal studies, the results of *in vitro* research using cellular systems should be part of these open access efforts as their scientific value will likely go beyond strict implementation of the 3Rs relevant to research with animals.
 - It is important that sharing of experimental designs and research results will in no manner compromise commercially sensitive information. Therefore, these different and in parts conflicting interests (open access versus property right concerns) must be seriously considered.

⁷ ter Riet G, Korevaar DA, Leenaars M, Sterk PJ, Van Noorden CJF, et al. (2012) Publication Bias in Laboratory Animal Research: A Survey on Magnitude, Drivers, Consequences and Potential Solutions. PLoS ONE 7(9): e43404. doi:10.1371/journal.pone.0043404

⁸ *ibid* p 1

⁹ *ibid* p 4

¹⁰ Gabriella Anderson, Haiko Sprott, and Bjorn R Olsen, ‘The Scientist’ January 15, 2013 <http://www.the-scientist.com/?articles.view/articleNo/33968/title/Opinion--Publish-Negative-Results/>



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Implementing the 3R Principles in Daily Research Practice – the Next Steps

3R-research activities appear to have arrived at crossroads: the major challenge is not only the development of novel methods and approaches to increase the impact of the 3Rs, but promote implementation of the 3Rs in the planning and execution of research projects, in which choices between using animals or alternative methods have to be made. A major aim is to raise the awareness of using the 3Rs and work toward their general implementation in state-of-the art biomedical research. It is also important to provide researchers with the proper incentives for implementing the 3Rs in their day-to-day research routine. To reach these aims, the following issues are in need of special attention at this stage:

1. At higher educational institutions, students need to be made aware of the 3R-philosophy as early as possible and throughout their curriculum. The 3Rs need to become part of the educational programme starting with bachelor students and continue to postdoctoral levels. Subsequently, the 3R knowledge needs to be continuously refreshed and updated, i.e. become an integral part of carrier development and lifelong learning.
2. The implementation and promotion of the 3Rs principles is a fundamental component of a culture of care within all research organizations. Senior management must establish a culture of responsibility and accountability where staff at all levels share a common commitment to: challenging necessity for animal use through rigorous ethical review, replacing animals through the use of alternative methods, reducing animal use through efficient experimental design and reducing suffering through refinement of experimental practice, animal husbandry and care.
3. The development of unified approaches with respect to dissemination of the 3R-philosophy within the research community and to general public is important. This can be supported by e.g. the establishment of institutional or (inter-) national 3R-Awards and other incentives.
4. Increased funding throughout Europe, to a level that represents a significant proportion of the total life science research funding budget, for research projects that seek to advance the development and validation of non-animal alternative methods or to otherwise advance implementation of the 3Rs. This should aid the implementation of experimentally sound alternative approaches, which help to replace, reduce and/or refine animal studies as part of state-of-art life sciences research.
5. Novel methods to assess the general validity and success of 3R research projects by both granting agencies and publishers are required.



Use of Higher Mammals in Research

Almost 85% of the animals used for medical, veterinary and basic research across Europe, covered legally by the EU Directive 2010/63/EU, are mammals. Additional, legally regulated animal models include fish, birds, amphibians and reptiles. This position paper discusses how the research community should meet the needs of higher mammals used for basic and applied research. Of the total number of animals used for research in the EU in 2008 (most recent statistics), 79.4% were rodents (primarily mice [59.3%] and rats [17.7%]). The majority of the other mammals were rabbits and pigs. Cats, dogs, non-human primates, equids and horses accounted together for less than 0.4% of all animals - see http://ec.europa.eu/environment/chemicals/lab_animals/pdf/sec_2010_1107.pdf

The role of mammals in research:

The history of medical and veterinary research shows that using mammals has been essential for many important medical breakthroughs as illustrated by few select examples:

- Mice and higher mammals played a key role in the development of the breast cancer drug Herceptin, which is based on a humanised mouse protein.
- Higher mammals, in particular non-human primates have played a critical role in understanding many aspects of biology relevant to human physiology and disease, from the Rhesus factor in blood to the development of Deep Brain Stimulation, a treatment strategy for Parkinson's disease and dystonia.
- Rabbits, dogs and cows were necessary for developing the human papillomavirus (HPV) vaccine, which is very effective in reducing incidents of cervical cancer in women.

Although the last hundred years have seen many medical breakthroughs, many more diseases remain incurable. For example, Alzheimer's and degenerative motor neuron diseases will become more prevalent as Europe's population continues to age. Research using mammalian species remains key to facing down some of these new challenges, which includes:

- Research on rodents aimed at breaking down the tau protein tangles associated with Alzheimer's disease. Furthermore, genetically modified mice help scientists to gain insight into the basic mechanisms that underlie normal organ development and physiology and the fundamental causes and potential prevention of human diseases.
- Non-human primates are also key models to study cognitive and fine-tuned motor abilities that are relevant for gaining insight into important human conditions such as neurodegenerative diseases, neural plasticity after damage to the nervous system, or the neural bases of the reward system and its pathologies, e.g. addiction.

- Studies using non-human primates also provide novel insight into infectious diseases that continue to claim many human lives (e.g. tuberculosis, malaria and HIV).
- Research on genetically modified pigs, another higher mammalian species, helps to understand and alleviate genetic and degenerative diseases such as Cystic Fibrosis and Duchene's muscular dystrophy.

Animal welfare issues:

Each species has different welfare needs that must be met when they are kept in captivity and used for scientific research. It is important that scientists address the specific needs of the species, strain or breed they have selected for their research. This will allow them to take best care of their animals and recognise signs of potential pain, suffering and/or distress. The greater sentience of mammals means that they need a different level of care, and that there must be a special focus on sound justification for using them for research. Some higher mammals may have needs that are difficult to meet in a laboratory setting, which must be considered in planning and evaluating such studies.

Before beginning a research project that uses animals, harm-benefit analysis must determine whether the potential suffering of animals is weighted by the expected gain of knowledge and/or benefits of the study. Benefits may include scientific, medical, and veterinary knowledge that can be translated to improving the understanding of normal and pathological mechanisms, which form the basis for developing scientific evidence-based treatments. Ultimately scientific knowledge is the major means whereby the health and welfare of humans and animals can be improved and protected. It is important to stress that advances in basic research which may, at the time of discovery, have little direct benefit to humans and animals, are an essential part of future clinical developments.

One of the key principles of animal welfare and good scientific practise is the 3Rs - Replacement, Refinement and Reduction of animals in scientific research (see Workshop 3). This principle is increasingly well-established and endorsed by the scientific community. It is also enshrined in both national and international legislations, such as the EU Directive 2010/63/EU. This principle and other ethical and legal constraints must be adhered to and respected wherever possible in all research using animals.

Choosing an experimental model:

A large variety of cellular and animal models are used in life-science research as the majority of medically relevant research topics cannot be investigated directly in human subjects for ethical reasons (see below) or because human tissues and cells are either not available or not suited. In veterinary and basic research, where understanding of animal development, physiology and/or pathophysiology is the goal, the use of animal models is often still the only valid approach. Whenever possible, studies using animals must be complemented by *in vitro* cell- or tissue models (of human and/or animal origin) and *in silico* computer simulations (based on data gathered using animal and/or cellular models). In any case, the use of animals must be limited to the necessary minimum. However, the Nuremberg Code

(1947) and the Declaration of Helsinki (1964; sixth revision 2008) state that experiments involving humans must be based on scientific knowledge, some of which will depend on experiments using animals. Thus, while many questions can be answered using our more distant evolutionary cousins, the analysis of closer relatives is also required to understand human conditions. Animal species that have contributed significantly to our understanding of living systems include invertebrates (e.g. fruit flies and nematode worms) and vertebrates (e.g. zebrafish, mice and non-human primates, typically macaque monkeys). Great apes - chimpanzees, bonobos, orang-utans and gorillas - are no longer used for invasive research in the EU.

Any ethically responsible and scientifically sound research relies on selection of the **most appropriate** animal model, which in return contributes to the 3Rs by improving the statistical reliability of the analysis and by likely achieving the best possible correlation with the study aims. While many basic biological questions can be answered using invertebrates or lower vertebrate models, mammalian models are required to study complex biological processes and model conditions relevant to both humans and mammals. In addition, the knowledge obtained by studying different key members of the animal kingdom is vital to understand the evolutionary relations between different species, to connect this knowledge, and to provide synergy in our insights and concepts of the fundamental processes of life.

Position Statements:

- Scientific research is a vitally important part of medical and veterinary progress and increases our basic understanding of the underlying complex biological processes. Research involving animals remains an essential aspect of medical and veterinary progress and for increasing our understanding of complex biological processes. As long as no scientifically validated animal-free alternative approaches exist, the use of animals must be allowed in a legally regulated framework as has been implemented in the EU (EU Directive 2010/63/EU) and Switzerland.
- The decision on which animal or non-animal model to use must be made on the basis of their suitability for the research aims in question. Research involving animals must be subject to careful ethical evaluation, which weighs potential harms to the animal with the expected benefits.
- All animals have intrinsic value and deserve the highest standards of animal welfare. The evolved nervous systems of higher mammals demands special attention with respect to their individual care and animal welfare. Researchers and their team members, veterinarians and caretakers, as well as the relevant administrative authorities, must continue to work to continuously improve animal welfare based on novel scientific findings, which includes social housing of animals in sufficient space. Experiments, which cause more severe levels of pain, suffering or distress should be replaced or at least reduced continuously and as much as possible. It is essential that all staff working with animals is adequately trained in the experimental techniques and welfare needs of the specific animal species entrusted to them. In particular,

they must be able to establish a positive and compassionate relationship with the animals under study.

- The high level of concern that the public has for the higher mammals used in research, in particular cats, dogs, pigs and non-human primates, requires that scientist embrace an equivalently high level of accountability and transparency in communicating and publishing their research.