Reporting of interventional animal studies in rheumatology

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SYSTEMATIC REVIEW

Quality of reporting of interventional animal studies in rheumatology: a systematic review using the ARRIVE guidelines

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Abstract

Aim: To systematically investigate the quality of reporting of published interventional animal studies in experimental rheumatology.

Methods: Original scientific publications in *Annals of the Rheumatic Diseases* (ARD) and *Arthritis and Rheumatism* (A&R) from January to December 2012 were identified. Studies were included if they used animal experimental model(s) and involved a treatment intervention. Data were extracted regarding disease type, animal model, intervention type and funding. Each study was assessed for quality of reporting, using the ARRIVE guidelines as a checklist.

Results: Forty-one studies (15 ARD, 26 A&R) were analyzed. Ethics approval was not reported or unclear in 22%. Randomization was not reported or unclear in 82.9% of the papers. Only 19.5% and 9.8% of papers reported attrition rate and important adverse events, respectively. Sample size calculation or allocation method was not reported in any paper. Only one study published negative results.

Conclusion: A number of key study design principles are poorly reported in experimental animal research investigating potential treatments in rheumatology. We support the widespread implementation of the ARRIVE guidelines in the rheumatology literature to promote the publication of manuscripts that allow rigorous appraisal of scientific quality.

Key words: ARRIVE, experimental rheumatology, systematic review.

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EDITORIAL

Increasing value and reducing waste in animal models of rheumatological disease

Preclinical studies are, by definition, performed with the purpose of improving human health. Yet promising findings from preclinical studies most often fail to translate to the clinic. The high drug attrition rate is startling; in cancer research, 95% of anticancer drugs fail at Phase I clinical trials,[1] and attrition rates in stroke drug discovery are over 99%.[2] Lack of reproducibility of preclinical studies may be an important driver of this failed translation. In oncology and cardiovascular research, industry scientists reported that in almost two-thirds of the projects (43 of 67) they were unable to replicate the major findings of published research.[3] In a separate study of 'landmark' publications in cancer research 89% (47 of 53) of preclinical findings could not be reproduced.[4] Some have suggested that the scientific reward system does not place adequate emphasis on investigators doing rigorous studies and reporting reproducible results.[5] These problems have led to increased focus on the importance of rigor in the design, conduct and reporting of studies in preclinical research[6,7] and the reproducibility of preclinical research.

A complex array of factors may contribute to a lack of reproducibility, including: poor reporting of methods; poor experimental design, such as a lack of methods to minimize bias (e.g., blinding and randomization); insufficient sample sizes; and inappropriate statistical analysis of results. Lack of prior publication of study protocols (including statistical analysis plans) may allow less scrupulous investigators to adopt a flexible approach to data analysis and exclusions, collecting several outcomes and conducting numerous statistical tests on the same data, and reporting only those which reach 5% significance and which allow a persuasive interpretation of their data consistent with their proposed hypothesis. Indeed, without the availability of a study protocol, it is impossible to know if the hypotheses being tested had even been articulated prior to data analysis, or whether in fact there has been over-interpretation of the results of studies that were designed to be hypothesis-generating.

Across a range of neurological conditions (Alzheimer's disease, multiple sclerosis, Parkinson's disease, intracerebral hemorrhage and focal ischemia) systematic reviews of the preclinical literature show that the reporting of measures to reduce the risk of bias is consistently low. Few studies report blinded assessment of outcome, randomization to group, allocation concealment or power calculations to determine sample size.[8] The impact of failure to report such measures has also been investigated, and non-blinded and non-randomized studies generally report greater drug efficacy than blinded or randomized studies, respectively.[9,10] We know also that underpowered experiments are unlikely to yield robust results and may lead to overstatement of efficacy[11] and this lack of statistical rigor will undoubtedly contribute to a failure to reproduce results from another laboratory.

Publication bias, where research that reaches publication is not representative of all research that is done, is also prevalent in the preclinical literature where neutral findings are likely to remain unpublished. Publication bias is exacerbated by the incentives to publish novel results. Estimates of the extent of this problem in preclinical stroke research suggests that it leads to a 30% overestimate of efficacy.[12]

Early work using systematic review and meta-analysis to assess the methodological quality of research and the impact of measures to reduce the risk of bias was conducted largely in the preclinical stroke research field.[13] Perhaps understandably, there was some resistance to the idea that these issues might be prevalent and important in other research fields. However, the application of these same tools to animal models of pain,[14] Alzheimer's disease,[15] spinal cord injury,[16] glioma[17] and multiple sclerosis,[18] has consistently found that the reporting of measures to reduce the risk of bias is low.

Against this background, the study by Ting *et al.* provides important evidence that these issues are prevalent in the field of experimental rheumatology. They searched two rheumatology journals, *Annals of the Rheu-*

Quality of Reporting of Interventional Animal Studies in Rheumatology

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BACKGROUND

- Studies of intervention require rigorous design and reporting to ensure the generation of reliable and valid data

- Deficiencies in the quality of human RCTs have been improved by the CONSORT guidelines

- *Recent attention to animal studies*[1]
  - *Of 271 experimental animal studies:*
  - *90% did not report randomisation or blinding*
  - *0% reported a sample size calculation*

1. Kilkenny *et al*. PLoS One 2009

BACKGROUND

- Poor quality animal studies may prevent the successful translation to clinical trials

- *2006 review of animal studies published in **7 leading, high impact** scientific journals*[2]
  - 1/3 of these translated at the level of human randomised trials
  - 10% were subsequently approved for use in patients

2. Hackam *et al*. JAMA 2006

BACKGROUND

- Akin to CONSORT, The Animal Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines (2010) were developed to improve the standards of reporting in animal experiments

	ITEM	RECOMMENDATION
Title	1	Provide as accurate and concise a description of the content of the article as possible.
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.
Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant.
Allocating animals to experimental groups	11	a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed.
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).
Statistical methods	13	a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.
RESULTS		
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing (this information can often be tabulated).
Numbers analysed	15	a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%[2]). b. If any animals or data were not included in the analysis, explain why.
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).
Adverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.
DISCUSSION		
Interpretation/ scientific implications	18	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 any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results[2]. c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.
Generalisability/ translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.

AIM

To systematically investigate the quality of published animal studies in the field of experimental rheumatology research, focusing on treatment interventions

ARD

A & R

Electronic search for experimental animal studies from Jan-Dec 2012 **(n= 277)**

Inclusion criteria:
Intervention studies
Original published papers

Exclusion criteria:
Mechanism studies
Reviews / Commentaries / Communications
Exclusively *in vitro* studies

n = 41

DATA EXTRACTION

random allocation

Reviewer 1 — n = 41

Reviewer 2 — n = 21

Reviewer 3 — n = 20

Disagreements were resolved via independent adjudicator to reach a consensus

RESULTS

- 41 studies included in the systematic analysis
  - 26 from Arthritis and Rheumatism
  - 15 from Annals of the Rheumatic Diseases
- 3 studies were concise reports
- Only 1 study published negative results

DISEASE TYPE	%
Inflammatory Arthritis	41.5
Systemic Sclerosis	19.5
SLE	17.1
Osteoarthritis	14.6
Polymyositis	2.4
Septic Arthritis	2.4
Periprosthetic Osteolysis	2.4

FUNDING	%
Government and or institution	68.3
Government / Institution / Industry	24.4
Industry only	2.4
No fund / unclear	4.9

ANIMAL MODEL	%
CIA	30.2
Bleomycin / Tight Skin	18.6
Lupus prone/bred mice (NZBxNZW)F1	14
K/Bxn model	4.6
HOCL injection	4.6
Adjuvant Arthritis Model	2.3
Antigen induced Arthritis	2.3
SCID mouse model	2.3
Collagenase injection	2.3
Knee transection	7.3
Medical Meniscus Destab.	2.3
Ig-transgenic mice	2.3
MMP deficient mice	2.3
C-protein induced myositis	2.3
Intramedullary implant	2.3

ETHICS

	REPORTED (%)	UNCLEAR (%)	NOT REPORTED (%)
Ethical statement - was ethical approvement attained?	78	9.8	12.2
Indicate the nature of the ethical review permissions, relevant licences or guidelines for the care and use of animals, that cover the research.	39	9.8	51.2

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Indicate the nature of the ethical review permissions, relevant licences or guidelines for the care and use of animals, that cover the research.	39	9.8	51.2

REPORTING

	REPORTED (%)	UNCLEAR (%)	NOT REPORTED (%)
Scientific background, study context and experimental rationale	100	0	0
Clearly describe objectives or state hypothesis	65.9	19.5	14.6
Explanation of the animal species and models being used to address the scientific objectives	75.6	12.2	12.2
Details of experimental procedures performed	82.9	7.3	9.8
Details of animal strain and species	53.7	29.3	17
Housing and husbandry	4.9	2.4	92.7
Study limitations incl. potential sources of bias, limitations of the animal model, and the imprecision associated with the results	12.2	0	87.8

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STUDY DESIGN

	REPORTED (%)	UNCLEAR (%)	NOT REPORTED (%)
No. of experimental and control groups	58.5	31.7	9.8
Randomisation	17.1	0	82.9
Assessor Blinding	29.3	12.2	58.5
Specify the total number of animals used in each experiment, and the number of animals in each experimental group.	31.7	14.6	53.7
Sample size calculation	0	0	100
Details of allocation method	0	9.8	90.2
Define the primary and secondary experimental outcomes assessed	39	31.7	29.3
Baseline data of animals – relevant characteristics and health status	0	0	100
Report the number of animals in each group included in each analysis and if any animals/data not included in the analysis, explain why	19.5	26.8	53.7

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STATISTICS

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Provide details of the statistical methods used for each analysis	75.6	17.1	7.3
Specify the unit of analysis for each dataset	78	12.2	9.8
Describe any methods used to assess whether the data met the assumptions of the statistical approach	4.9	0	95.1
Outcomes and estimation - Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).	39	14.6	46.3

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HARM

	REPORTED (%)	UNCLEAR (%)	NOT REPORTED (%)
Give details of all important adverse events and any subsequent modifications to the experimental protocols	9.8	2.4	87.8

SUMMARY

- Fundamental concepts in study design are poorly reported
- Poor quality of reporting: reduced generalisability and reproducibility of studies
- Over-representation of positive studies
- Selective outcomes or analysis reporting biases
  - In 61% there was a failure to clearly define experimental outcomes *a priori* suggesting that only positive outcomes had been reported

LIMITATIONS

- This study analyses the quality of *reporting* of animal studies
- Small series – larger numbers necessary for statistical analysis and deeper understanding of factors affecting reporting
- Only used 2 journals – although top ranking in rheumatology
  - ? focus on specific experimental journals
- Unable to make a comment regarding translation

CONCLUSIONS

- Published animal studies investigating potential treatments in the top 2 rheumatology journals exhibit poor reporting of key design principles

- The use of the ARRIVE guidelines is hoped to improve the quality of reporting, and optimise the use animals in research to advance scientific knowledge

FUTURE DIRECTIONS

- Promote Transparency in Reporting
  - Demanding robust reporting of ethical approval and licensing
- The effect of endorsement of the ARRIVE guidelines
  - Will ARRIVE improve study quality?
  - Will this improve translation?
- Animal trial registry
  - Access to all relevant data
  - Diminish publication and selective reporting biases
  - Reduce squandering of animals and premature human trials

WHAT HAS HAPPENED SINCE?

WHAT HAS HAPPENED SINCE?

- (Intra-departmental backlash)

WHAT HAS HAPPENED SINCE?

- Both journals endorse* ARRIVE

WHAT HAS HAPPENED SINCE?

- Both journals endorse ARRIVE
- ARRIVE alone is not enough

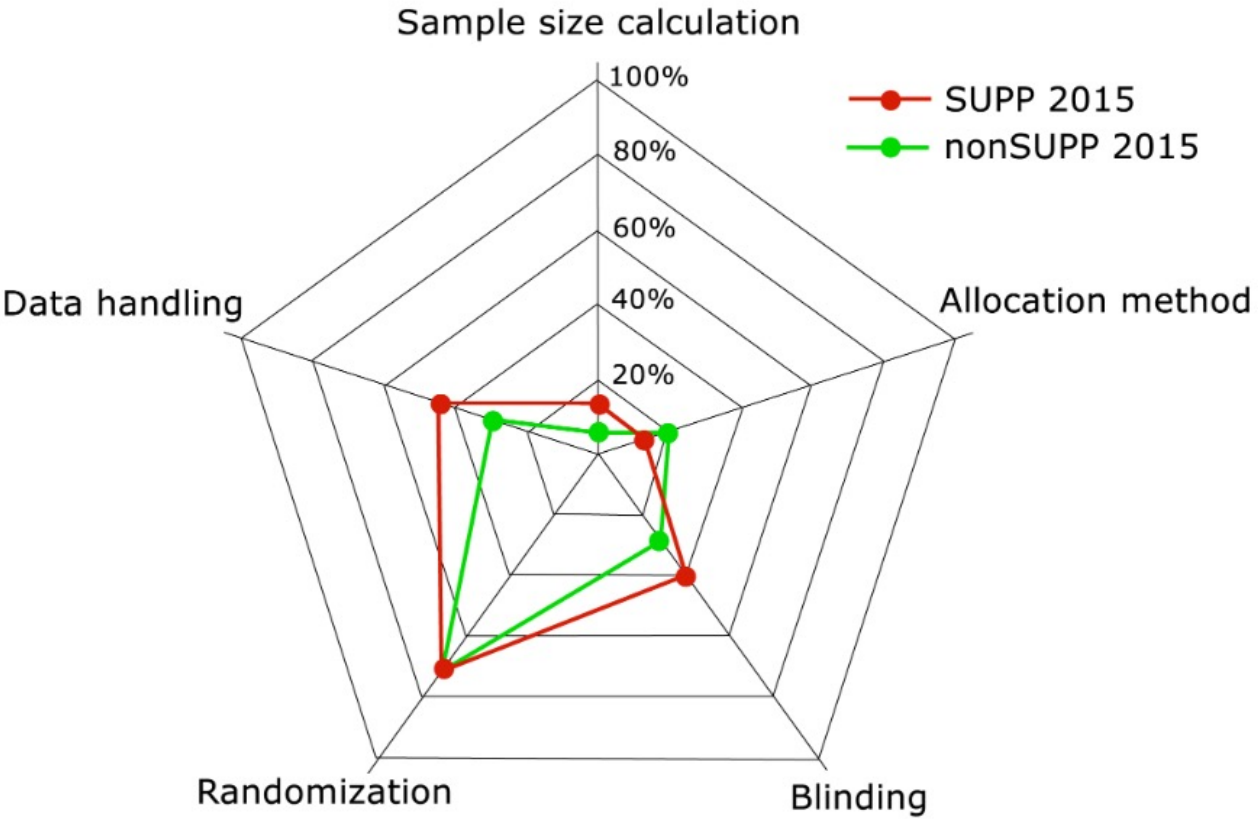

Fig 3. Radar plot of ARRIVE checklist sub-items associated with bias reported in ARRIVE supporting (SUPP) and non-supporting (nonSUPP) journals in 2015.

https://doi.org/10.1371/journal.pone.0197882.g003

WHAT HAS HAPPENED SINCE?

- Both journals endorse ARRIVE
- ARRIVE alone is not enough
- ARRIVE 2.0

PERSPECTIVE

The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: AA is the editor in chief of the British Journal of Pharmacology. WJB, ICC, and ME are authors of the original ARRIVE guidelines. WJB serves on the Independent Statistical Standing Committee of the funder CHDI foundation. AC is a Senior Editor for PLOS ONE. AC, CJM, MM, and ESS were involved in the

Abstract

Reproducible science requires transparent reporting. The ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) were originally developed in 2010 to improve the reporting of animal research. They consist of a checklist of information to include in publications describing in vivo experiments to enable others to scrutinise the work adequately, evaluate its methodological rigour, and reproduce the methods and results. Despite considerable levels of endorsement by funders and journals over the years, adherence to the guidelines has been inconsistent, and the anticipated improvements in the quality of reporting in animal research publications have not been achieved. Here, we introduce ARRIVE 2.0. The guidelines have been updated and information reorganised to facilitate their use in practice. We used a Delphi exercise to prioritise and divide the items of the guidelines into 2 sets, the "ARRIVE Essential 10," which constitutes the minimum requirement, and the "Recommended Set," which describes the research context. This division facilitates improved reporting of animal research by supporting a stepwise approach to implementation. This

WHAT HAS HAPPENED SINCE?

- Both journals endorse ARRIVE
- ARRIVE alone is not enough
- ARRIVE 2.0
- Animal trial registries

PLOS BIOLOGY

COMMUNITY PAGE

Refining animal research: The Animal Study Registry

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: All authors of this manuscript are employed at the BfR and are working for the Bf3R, except Matthias Greiner who works at the Department Exposure of the BfR. The Animal Study Registry was developed and is hosted by the German Federal Institute for Risk Assessment (BfR). The BfR is a governmental institution within the sphere of the Federal Ministry

Abstract

The Animal Study Registry (ASR; www.animalstudyregistry.org) was launched in January 2019 for preregistration of animal studies in order to increase transparency and reproducibility of bioscience research and to promote animal welfare. The registry is free of charge and is designed for exploratory and confirmatory studies within applied science as well as basic and preclinical research. The registration form helps scientists plan their study thoroughly by asking detailed questions concerning study design, methods, and statistics. With registration, the study automatically receives a digital object identifier (DOI) that marks it as intellectual property of the researcher. To accommodate the researchers concerns about theft of ideas, users can restrict the visibility of their registered studies for up to 5 years. The full content of the study becomes publicly accessible at the end of the embargo period. Because the platform is embedded in the infrastructure of the German Federal Government, continuity and data security are provided. By registering a study in the ASR, researchers can show their commitment to transparency and data quality to reviewers and editors, to third-party donors, and to the general public.

Introduction

The scientific community is striving for greater transparency in animal research as a measure to enhance the reproducibility of results and to gain more knowledge from animal studies.

Missing efficacy was found to be the main reason for clinical failure of drug candidates [1–4], and irreproducibility of preclinical data was blamed to be the dominating cause. Thus, scientific progress and development of new medical therapies are and will be slowed down by poor quality of preclinical data. The problems regarding the reproducibility of animal studies appear in all bioscientific disciplines studying animals [5]. Therefore, changes are needed to improve the reproducibility within biosciences.

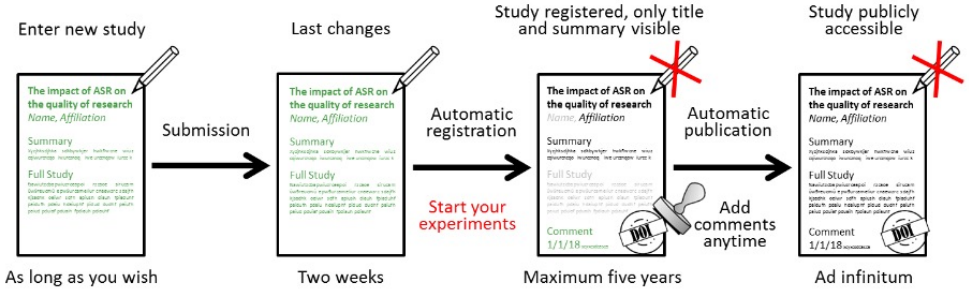
Numerous factors contribute to the irreproducibility of research studies. Biological heterogeneity and complexity as well as the use of nonstandard methods or technologies certainly are

Animal Study Registry

Animal Study Registry is an online registry for scientific studies involving animals conducted around the world. It is operated by the German Centre for the Protection of Laboratory Animals (Bf3R) at the German Federal Institute for Risk Assessment (BfR). The registry was launched as a reaction to the reproducibility crisis and provides scientists a platform to register an exact study plan prior to the start of experiments in order to prevent selective reporting. This allows reviewers or other scientists to compare the initially registered contents with the final publication. Thereby, Animal Study Registry encourages transparency, reproducibility, and animal welfare.

Register your study in Animal Study Registry

Take all the time you need to prepare the registration of your study in Animal Study Registry. As long as your study is in preparation, you can save all changes and come back to it anytime you want. Once your study is submitted, you can still decide to change or retract it within two weeks from the submission date. After this period, the registration becomes binding and your study receives a DOI (Digital Object Identifier) number which marks your study as your intellectual property. From this date on you can only add comments to your study. Our platform allows registration of a study without making it immediately publicly accessible. You can restrict the visibility of your study for a period of up to five years. During this embargo period, your study will appear in Animal Study Registry only with its title, your institution and optionally your name, accompanied by a short summary. At the end of the embargo period, your study will automatically become fully publicly accessible. Please have a look at our sample study 10.17590/asr.0000091.



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"We can **increase transparency** and **improve quality** of research!"

WHAT HAS HAPPENED SINCE?

- Both journals endorse ARRIVE
- ARRIVE alone is not enough
- ARRIVE 2.0
- Animal trial registries
- ANZMUSC Basic Science SIG ✅