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Pet Research Approval is based on Confidence than on Proof of Scientific Rigour

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Abstract

A growing body of evidence raises concerns about the scientific validity and reproducibility of published research findings due to the substantial risk of bias in preclinical animal studies. Systematic reviews discovered poor reporting rates of bias prevention techniques (such as randomization, blinding, and sample size calculation) in the published literature and a link between these low reporting rates and exaggerated treatment effects. It might be possible to identify bias risks sooner, before the research has been conducted, if the majority of animal research were subject to ethical or peer review. For instance, animal studies are authorised in Switzerland based on a harm-benefit analysis and a full explanation of the study procedure. Therefore, we compared the reporting rates of the same measures in a representative sub-sample of publications (n = 50) with the rates at which the use of seven basic measures against bias (allocation concealment, blinding, randomization, sample size calculation, inclusion/exclusion criteria, primary outcome variable, and statistical analysis plan) were described in applications for animal experiments submitted to Swiss authorities (n = 1,277). In applications for animal experiments, measures against bias were disclosed at extremely low rates, ranging on average from 2.4% for the statistical analysis plan to 19% for the primary outcome variable, and from 0.0% for the calculation of the sample size to 34% for the statistical analysis plan in publications from these experiments. We found a weak positive correlation between the internal validity scores (IVS) of publications and applications (Spearman's rho = 0.34, p = 0.014), indicating that the rates of describing these measures in applications partially predict their rates of reporting in publications. The IVS was calculated based on the proportion of the seven measures against bias. These findings suggest that key information about experimental design, which establishes the scientific validity of the findings, is missing from the authorities licencing animal experiments. This information may be crucial for the weight given to the research's benefits in the harm-benefit analysis. Applications for animal experiments may frequently be allowed based on implicit confidence rather than explicit evidence of scientific rigour, similar to articles getting accepted for publication despite poor reporting of measures against bias. Our results cast considerable doubt on the peer-review process for scientific publications as well as the current authorization process for animal studies, which over time may damage the validity of research. One viable method to change the system is to transition from the authorization processes that are already in place in many nations to a preregistration system for animal research. This would help to prevent needless harm to animals for fruitless research as well as improve the scientific quality of data from animal trials.

Author synopsis

Scientific rigour, which includes steps to prevent bias, such as randomising the assignment of animals to treatment groups and evaluating outcome measures without being aware of the treatment groups to which the animals belong, is necessary for the scientific validity of research findings (blinding). The systematic studies indicated that inadequate reporting was linked to greater treatment effects, indicating bias, and that safeguards against bias are infrequently reported in publications. Here, we looked into the possibility of predicting bias risk from study protocols submitted for ethical review. In study protocols submitted for approval in Switzerland as well as in publications emerging from these studies, we looked for mention of seven fundamental precautions against bias. Both in study procedures (2%-19%) and in publications (0%-34%), measures against bias were indicated at very low rates. The rates at which measures against bias were specified in study protocols predicted the rates at which they were reported in publications, according to a weakly positive connection that we discovered. Our findings show that the approval of animal studies is frequently based more on scientific rigour than on evidence of confidence, which may impair the validity of the research and cause undue injury to the animals.

Introduction

A key component of the scientific process is reproducibility, which sets it apart from anecdotal evidence. Reproducibility is important for the advancement of both basic and practical research, and it can be severely inhibited by poor reproducibility. Nevertheless, mounting data suggests that repeatability is subpar across several life sciences domains. Prinz and colleagues found significant discrepancies (65%) between published and in-house data in the fields of oncology, women's health, and cardiovascular diseases. Oncologists from Amgen could only confirm 6 out of 53 published findings. Of more than 100 compounds that showed promising effects on amyotrophic lateral sclerosis, only 8 out of 18 studies could be replicated (ALS), None of

the preclinical experiments' results held true when they were repeated by the Cambridge-based ALS Therapy Development Institute. Poor reproducibility, however, comes with major ethical issues in addition to being a loss of time and resources for fruitless study. While in basic and preclinical animal research, it may result in unjustified injury to experimental animals, irreproducibility of preclinical research may expose patients to unwarranted risks in clinical research. The internal and external validity of experimental results are both accounted [1-5] for by the experimental design and conduct, which are significantly dependent on reproducibility. External validity is the extent to which findings are transferable to different environments, experimenters, study populations, and even different animal strains or species (including humans). As a result, it also establishes if the findings are repeatable among replication investigations (i.e., across various labs, experimenters, study populations, etc.). Internal validity relates to how much a causal relationship between an experimental treatment and outcome is justified, and it vitally depends on scientific rigour, or how much systematic bias is minimised in the experimental design and conduct. Poor internal validity resulting from a lack of scientific rigour has been proposed as another important factor in the low repeatability of animal studies. There are many different types of bias (such as selection bias, performance bias, and detection bias), and there are specific ways to reduce them (such as randomization, blinding, and sample-size calculation). Publications must include adequate material on experimental design and conduct, including steps taken against bias risks, to enable replication of findings and to assess the internal validity of studies, for example, in the peer review process. Systematic evaluations, however, often discovered a low prevalence of reporting of safeguards against bias hazards (sometimes referred to as reporting) in papers including animal [6-8] research. As a result, reporting for allocation concealment ranged from 8% to 55.6%, for blinded outcome assessment from 3% to 61%, for randomization from 7% to 55%, and for sample size calculation from 0% to 3%. Low reporting rates have been used as justification for a lack of scientific rigour. In fact, a number of systematic evaluations discovered links between inaccurate reporting and exaggerated treatment effects. Thus, reporting requirements have developed into a key tool in the battle against the possibility of bias in animal research. Although more than 1,000 journals endorsed the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) developed by the UK-based NC3Rs (National Centre for the Replacement, Refinement & Reduction of Animals in Research), this did not result in a significant improvement of reporting in animal studies. Although there is still much room for improvement, Macleod and colleagues have discovered that reporting has increased over the past decades, suggesting that awareness is indeed rising. The majority of the research on the internal validity of animal studies has been centred on reporting in academic journals. However, the majority of published research has undergone peer review when funding applications are made, and in some nations (such as Switzerland and Germany), specific animal experiments are authorised by local, state, or federal authorities. The approval of animal experiments, for instance, is based on a clear harm-benefit analysis in Switzerland, where any harm done to the animals is weighed against the anticipated benefit (knowledge gained) of the experiment. Risks of bias may influence the weight given to the predicted benefit of a study in the harm-benefit analysis because the advancement of knowledge is significantly dependent on the scientific validity of the findings. A thorough harm-benefit analysis therefore requires knowledge of bias hazards and the countermeasures employed to counteract them. In the current study, we compared the rates at which these measures were described in applications (for purposes of simplicity hereafter also referred to as reporting) with the rates of reporting of the same measures in a representative sub-sample of publications (n = 50) resulting from animal experiments. We did this by screening applications for animal experiments submitted to the cantonal authorities in Switzerland (n = 1,277) for evidence of the use of measures to avoid risks of bias. This allowed us to compare the evidence presented in scholarly journals with the evidence of scientific rigour provided to the authorities when approving animal research for the first time, and to determine whether inadequate reporting in experiment applications predicts inadequate reporting in the scientific literature.

Materials and Method

Sampling process

An anonymized database of all applications submitted in Switzerland since 1983 was obtained from the FSVO and contained applications for animal research (Form A, S1 Text). A contract between the FSVO and the authors of this study, which guaranteed secrecy to the applicants, was the basis for access to applications stored by the FSVO. Based on previously established inclusion and exclusion criteria, applications were chosen. Thus, only new applications submitted in the years 2008, 2010, and 2012 were considered, and applications relating to disease diagnosis, education and training, and the protection of people, animals, and the environment through toxicological or other safety tests mandated by law were automatically disregarded. These requirements were completed by 1590 applications, which underwent a rigorous screening process.

Checklist

A checklist was developed (S2 Text) based on checklists used in earlier studies examining the use of methods to reduce risks of biases as reported in the published literature in order to assess risks of bias in the experiments mentioned in the applications. We limited the items on our checklist to those that are generally relevant to all types of experimental studies and can be evaluated objectively without specialised knowledge of the research topic. We also included the seven items that we found in the [9] literature the most frequently: allocation concealment, blinded outcome assessment, randomization, formal sample size calculation, inclusion and exclusion criteria, a primary outcome variable, and a statistical analysis plan.

Discussion

This study examined whether poor reporting in applications for animal experiments, that is, before the studies have actually been conducted, is a predictor of poor reporting in the scientific literature. This was done in light of the low reporting rates in publications of animal research and evidence suggesting that poor reporting may reflect a lack of scientific rigour. For two reasons, the study was limited to animal studies that were permitted in Switzerland. First, Switzerland has a mechanism for authorising animal experiments that calls for a thorough explanation of the study methods for each one that is anticipated. These study procedures serve as the foundation for the harm-benefit analysis that determines whether or not to approve specific studies. Second, The Swiss Federal Food Safety and Veterinary Office (FSVO) provided access to all applications for animal studies via their online platform (e-tierversuche), which allows scientists to submit their applications for animal experiments and engage with the authorities. It is commendable that the FSVO approved this meta-research given the unprecedented open access to application forms for animal studies. According to Chan, obtaining this kind of support

for clinical trial protocols for meta-research has historically been challenging for reasons of secrecy. Access to the application forms was accessible without breaching confidentiality, as stated in the Materials and Methods.

Results

A final sample of 1,277 applications for animal experiments that were accepted by Swiss cantonal authorities in the years 2008, 2010, and 2012 were included in our database. A statistical analysis strategy, inclusion and exclusion criteria, allocation concealment, blinded outcome assessment, sample size calculation, inclusion and exclusion criteria, primary outcome, and blinded outcome assessment were used to evaluate the scientific rigour of the study. The internal validity score, which was the main outcome variable for the statistical analysis of the impacts of different study descriptors on reporting rates, was produced in addition to individually examining each item.

Acknowledgments

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