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EDITORIALS

Improving the conduct, reporting, and appraisal of animal research

All stakeholders must act decisively to fix endemic problems

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Preclinical animal studies aim to establish safety and efficacy before patients are exposed to new treatments. However, the translational success rate from animal studies to humans is quite low, and the non-reproducibility of preclinical studies ranges between 51% and 89%.[1] The inadequate conduct, reporting, and evaluation of animal research underpinning human trials is one reason why big promises of better outcomes for patients so often remain unfulfilled.

Improvements in the design, registration, reporting, and transparency of animal studies are urgently needed. To achieve this, we need a cultural change in which researchers are rewarded for producing valid and reproducible results that are relevant to patients, and for doing justice to the animals being used. The MVA85A vaccine story (doi:10.1136/bmj.j5845),[2] is an example of a case where a more thorough analysis of preceding animal studies could have resulted in better targeting of resources in human studies.[2 3]

What are the essential next steps to make animal research more fit for purpose as a valuable and reliable forerunner to clinical research in humans? Systematic reviews of animal studies have been instrumental in exposing the current limitations within preclinical evidence and identifying reasons for translational failure.[4-6] For example, human clinical trials initiated after positive results of individual animal studies have found zero benefit or even harm—an outcome that could have been prevented by a careful systematic review of all animal studies before the launch of the clinical trial.[3 7] This is the first step up, akin to the improvements in reporting of clinical trials prompted by the establishment of the Cochrane collaboration in 1992. Integrating systematic reviews of animal studies into the Cochrane framework would boost cross fertilisation with clinical systematic reviews.

Systematic reviews of animal studies have also exposed the high risk of reporting biases in this research, especially publication bias and selective reporting of outcomes. Prospective registration of animal study protocols is crucial to prevent these biases. Registration of clinical trials is commonly mandatory, but it remains rare for animal studies. This will hopefully change with the recent launch of www.preclinicaltrials.eu, a registration platform for animal studies.

Journals should make prospective registration a condition of publication and should provide their editors and reviewers with tools to help identify selective outcome reporting and HARKing (hypothesising after results are known) in submitted manuscripts. Funders of animal research should also demand registration, along with high quality open access publication of results or registration of full methods and outcome data. If final methods and results are not made public in a timely manner, future funding should be withheld.

Systematic reviews of animal studies should become commonplace. Importantly, they must be high quality. This means prospective registration of all review protocols, enabled by a recent extension to PROSPERO, the registry of systematic reviews in health; use of unbiased methods, as assessed by validated methods such as the ROBIS (risk of bias in systematic reviews) tool; and full reporting using the forthcoming extension to PRISMA (preferred reporting items for systematic reviews and meta-analyses).

When preclinical evidence is critical to a decision to start a clinical trial, ethics committees should demand that all preceding animal studies are systematically reviewed, including (if possible) an assessment of the certainty of the evidence according to GRADE principles.[8] Regulatory bodies such as the US Food and Drug Administration and the European Medicines Agency should also become more demanding regarding the robustness of the preclinical evidence that underpins licensing applications. Since synthesis of preclinical evidence is a highly specialised field, an external expert should lead the quality assessment of evidence summaries and advise regulators on their interpretation.

The poor reporting of methods and findings must be addressed in both primary animal studies and subsequent systematic reviews. The ARRIVE (animals in research: reporting in vivo experiments) guidelines for reporting in vivo experiments,[9] embedded in the instructions for authors by at least 600 journals since 2010, had in 2014 not resulted in the hoped for improvements in study reporting.[10 11] And as long as it is possible

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to publish in high impact factor journals without having to satisfy the ARRIVE guidelines, current practice is unlikely to change. Journals should take responsibility for full and transparent reporting of animal studies, including flexible or even absent word limits for online reporting of methods. Editors should make sure that articles do not enter the review process without completion of ARRIVE or other official reporting guidelines. A recent roundtable with editors, funders, and academia concluded that academic institutions also need to act now if scientists are to be skilled in reliable and reproducible studies.[12]

By definition, to research means to re-search. A systematic review of preclinical animal studies is genuine re-search and a solid basis for subsequent clinical trials. If the responsible bodies mentioned above succeed in making a culture change, demanding high quality reporting and systematic reviews of animal studies, the potential of animal studies to transform human health will be realised.

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