

# The need for registration of preclinical studies

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## Abstract

In contrast to controlled clinical trials, findings of preclinical studies are not available. The road from laboratory discovery to usable therapy is still long and windy. Many preclinical studies have not been replicated by the pharmaceutical sector, the costs of clinical trials are rising, and many trials fail due to insufficient animal model evidence. To improve cross-talk between scientists and to develop rational strategies to move therapies into the clinic, scientists are going to be invited to register their experiments. The proposed registration and availability of preclinical research findings, published in the June 2012 issue of *Nature Biotechnology* by Kimmelman and Anderson, would facilitate a clinical translation process that would benefit the scientific community. In particular, to support clinical trial development programs, they propose the design and registration of controlled *in vivo* animal studies testing toxicity, toxicology, and disease response with a similar structure to controlled clinical trials.

**Keywords:** Preclinical research, Clinical trials, Translational research, Registration

In recent years, the registration of clinical trials and deposition of controlled trial results, even those that are negative and inconclusive, has become a must.<sup>1</sup> Preclinical study results, by contrast, are not deposited or registered.

We all know how hard it is to publish negative results from scientific studies. Especially in the field of cancer therapeutics, the vast majority of false findings are seen as invalid because it is difficult to translate them into valuable therapies to cure patients. 'Messy' results of fascinating and highly promising laboratory studies have a long road from bench to bedside.

Nowadays, it is almost impossible to obtain a grant from bodies such as the German Research Foundation, the German Federal Institute for Drugs and Medical Devices, or the National

Institutes of Health based on pure basic science without a translational angle. Although early reports in the peer-reviewed literature are tentative and their findings may later be found to be incorrect or even spectacularly wrong, they are potentially valuable and useful.

## The proposal to register preclinical trials and report their results

A correspondence article published by Kimmelman and Anderson in the June 2012 issue of *Nature Biotechnology* urged 'funding agencies, journals, foundations and academic institutions to devise policies that promote registration and reporting of preclinical results' with the aim of supporting clinical trials.<sup>2</sup> In particular, the authors suggested limiting their proposal to controlled *in vivo* animal studies directed at testing toxicity/toxicology and disease response since these studies have a similar structure to controlled clinical trials.<sup>2</sup> They pointed out that registering and reporting of preclinical studies would partly decrease concerns about human protection and inefficiency in the clinical research enterprise by minimising failures in translating findings from basic research into new medical therapies. If registration and public deposition of preclinical results ('good disclosure practice') were canonised as ethical principles, good disclosure practice 'may respect the altruism of human subjects by helping ensure that preclinical studies see the light of day'.<sup>2</sup> Since publication is the first step in a process where findings from isolated settings are taken up and applied by practitioners, nonpublication may evoke 'concerns encountered by human volunteers losing their moral justification'.<sup>2</sup>

Further, Kimmelman and Anderson anticipate the protection of downstream users – patients and institutions – having particular interests in free access to findings. Research communities benefit greatly from the free flow of scientific information, and a lack of and delay in timely evaluation of

preclinical observations can hamper researchers' ability to gain valuable insight from failures in clinical development. 'In the absence of a good disclosure practice, researchers coming forward with unfavorable findings are at a reputational and funding disadvantage relative to those withholding them', leading to biased reporting.<sup>2</sup> Biased reporting may potentially harm patients by mispresenting treatment recommendations. In addition, biased reporting may prevent healthcare providers from assigning resources according to the best published evidence.<sup>2</sup>

### **Disclosure of preclinical trial data should help reduce publication bias**

Disclosure of preclinical trial data may enhance institutional access to evidence, thereby decreasing the high rates of attrition during human testing. Only 11% of new products entering phase 1 clinical trials are licensed; for cancer and neurological disorders, the figures are closer to 5 and 8%, respectively.<sup>3</sup> Longitudinal studies have demonstrated that most highly promising preclinical findings resist the translation process. These failures should provoke a hunt for strategies that help ensure that volunteers are not needlessly enrolled in trials and that 'scarce research resources are not squandered'.<sup>2</sup>

Unfortunately, unpublished findings cannot contribute to the distillation of knowledge. If the unpublished data differ substantially from published work, conclusions may not reflect adequately the underlying biological effects being described.<sup>3</sup> Using Egger regression and trim-and-fill analysis, Sena and colleagues<sup>4</sup> clearly showed that publication bias was highly prevalent in animal studies of stroke. Their trim-and-fill analysis suggested that publication bias may account for around one-third of the efficacy reported in systematic reviews, with reported efficacy falling from 31.3 to 23.8% after adjustment for publication bias. Selective publication spoils appraisal of promise by limiting the ability of decision makers to assess the totality of preclinical evidence. This can lead to overestimation of treatment effects, as indicated by recent studies which demonstrated inflation of effect sizes by 30% due to publication bias.<sup>4</sup> It is likely that publication bias has an important impact in other animal disease models too.

Further, if the dissemination of information from animal experiments is not shared within the broader research community, the burdens imposed on animals in preclinical experiments are wasted, raising ethical concerns about animal welfare.<sup>2</sup>

The reporting of animal findings also enables secondary analyses. Retrospective analysis of pooled preclinical data may address many questions, thus advancing knowledge about translation itself. For instance, retrospective analysis of AstraZeneca's unsuccessful stroke drug disufenton sodium indicated the lack of activity of this free radical trapping drug in hypertensive rats.<sup>5</sup> Given that most stroke patients are hypertensive, this finding may help to explain the failure in the clinical trials. Although the compound was shown to be neuroprotective in experimental stroke, there was a negative publication bias. That bias may have resulted in an overestimation of efficacy, implying that efficacy in healthy, male, adolescent animals is a poor predictor of success in clinical trials. Thus, Bath and coworkers<sup>5</sup> suggested the use of preclinical meta-analysis before initiation of future clinical trials. Indeed, the decision to proceed to clinical study should be based on a thorough and systematic review of the animal data.

### **Implementing the proposal to disclose preclinical trial data**

Unfortunately, cost may hinder implementation of the proposal since maintaining preclinical study registries may be expensive. 'Registries entail administrative costs (the 2007 budget for clinicaltrials.gov [<http://clinicaltrials.gov/>] was \$3 million) and compliance expense for investigators'.<sup>2</sup> 'Well-documented flaws in reporting and compliance with trial registries would likely be recapitulated in preclinical registries'.<sup>2,6</sup>

Despite cost concerns, the benefits should outweigh the costs of registration of controlled preclinical studies. Kimmelman and Anderson recommended the use of models less costly than clinicaltrials.gov, such as those utilised to promote deposition of genomic and microarray data.<sup>2</sup> For example, high-impact biomedical journals could encourage future good disclosure practices by requiring authors of preclinical experiments to state that a complete summary of preclinical evidence exists in a public database.<sup>2</sup> Preclinical trial registries may begin with a series of modest steps affording opportunities to test and refine animal models establishing necessary elements for data inclusion. Scientists working on congenital muscular dystrophy can already register their experiments on line (<http://curecmd.org/scientists/preclinical-trial-registry>). Hopefully, more websites like this will become available. These should improve cross-talk between scientists and help develop rational strategies to move therapies into clinic.

## Conclusion

The proposed registration and reporting of preclinical research findings will facilitate clinical translation, shortening the long road from laboratory discovery to usable therapy.

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## Author information

**Dr Sanja Pavlica** received a PhD in biochemistry in 2005 from Leipzig University and performed postdoctoral studies in neurochemistry. From August 2007 to 2012, she was Head of the Neuro/Liver Group at the Department of Cell Techniques and Applied Stem Cell Biology, Biotechnological and Biomedical Center, Leipzig University, where she worked in the field of

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