European legislation
Impact on the scientific use of animals

"Mind the method!" – a longitudinal assessment of methodological soundness and quality of reporting of ALS research on the SOD1G93A mouse

Franco, N., Fernandes, J,, Grierson, A., Furley, A., Olsson, A.

Introduction
Persistent translational failure of candidate drugs for Amyotrophic Lateral Sclerosis (ALS) has raised criticism over the predictive value of current animal models. However, it has been argued that clinical trials are being based on false-positive results from poorly designed, underpowered animal studies (e.g. Perrin,2014. Nature 507:423-425; Scott et al, 2008. Amyotroph Lat Scl 9(1):4-15). The ALS research community responded by issuing guidelines, in 2007 (Ludolph et al. Amyotroph Lat Scl 8(4):217-223) and 2010 (Ludolph et al. Amyotroph Lat Scl 11(1-2): 38-45), for carrying out and reporting animal studies. We present results from a systematic review of scientific and reporting standards of ALS studies published both before and after publication of said guidelines.

Methods
A sample of 382 studies – published in 2005, 2009, 2011 and 2013 – on the SOD1 mouse model of ALS was retrieved. Studies were classified as either "preclinical" (n=72) or "proof-of-concept" (n=310), and reporting of relevant research parameters and experimental design was assessed.

Results
Preclinical studies reported significantly more details on central variables than proof-of-concept studies, namely sex of the animals (69% vs. 46%, $p<0.001$), number of transgene copies (78% vs. 62%, $p<0.05$) and genetic background (86% vs. 74%, $p<0.05$). Reporting of measures to minimize bias was also higher for preclinical studies, namely random assignment of animals (46% vs. 6%, $p<0.001$) and blinding of observers (44% vs. 24%, $p<0.001$). Only 53% of all studies used animals of both sexes. Most preclinical studies (N=71) used fewer ($\bar{x}$=13,6; SD=6,7) animals than the minimum of 24 recommended in the guidelines. No differences were found for these parameters between before and after the issuing of guidelines.

Conclusions
Biases in animal data resulting from poor quality research prevent a fair assessment of the actual translational value of ALS models. Results must be reproducible in the same species before moving to humans, which can only be achieved if animal studies comply with best practice (e.g. through blinding and randomization). While our results suggest preclinical studies are more compliant with best practice than proof-of-concept studies, guidelines for ALS did not appear to have had an

effect yet, suggesting more needs to be done to improve the planning, execution and reporting of mouse studies, a central requisite for making preclinical trials more reliable.

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