THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ioannidis JPA, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62227-8.

Additional web references

Development of protocols and improvement of designs

Laine C, Horton R, DeAngelis CD, et al. Clinical trial registration: looking back and moving ahead. *Lancet* 2007; **369:** 1909–11.

Fleming TR. Addressing missing data in clinical trials. *Ann Intern Med* 2011; **154:** 113–17.

Brooks P, Hochberg M, and the ILAR, and the OMERACT. Outcome measures and classification criteria for the rheumatic diseases. A compilation of data from OMERACT (Outcome Measures for Arthritis Clinical Trials), ILAR (International League of Associations for Rheumatology), regional leagues and other groups. *Rheumatology (Oxford)* 2001; **40:** 896–906.

Kilkenny C, Parsons N, Kadyszewski E, et al. Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS ONE* 2009; **4:** e7824.

Macleod M. Why animal research needs to improve. *Nature* 2011; **477:** 511.

van der Worp HB, Howells DW, Sena ES, et al. Can animal models of disease reliably inform human studies? *PLoS Med* 2010; **7:** e1000245.

Panel 1

Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. *PLoS Med* 2007; **4:** e78.

Wen J, Ren Y, Wang L, et al. The reporting quality of meta-analyses improves: a random sampling study. *J Clin Epidemiol* 2008; **61:** 770–75.

Davies S. The importance of PROSPERO to the National Institute for Health Research. *Syst Rev* 2012; **1:** 3.

Research workforce and stakeholders

Greenland S. Commentary: Addressing corporate influence through ethical guidelines. *Int J Epidemiol* 2008; 37: 57–59, discussion 65–68.

Greenland S. Accounting for uncertainty about investigator bias: disclosure is informative. *J Epidemiol Community Health* 2009; **63:** 593–98.

Lathyris DN, Patsopoulos NA, Salanti G, Ioannidis JP. Industry sponsorship and selection of comparators in randomized clinical trials. *Eur J Clin Invest* 2010; **40:** 172–82.

Ioannidis JP. An epidemic of false claims. Competition and conflicts of interest distort too many medical findings. *Sci Am* 2011; **304:** 16.

Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Ghost authorship in industry-initiated randomised trials. *PLoS Med* 2007; **4:** e19.

Bross ID. How to eradicate fraudulent statistical methods: statisticians must do science. *Biometrics* 1990; **46:** 1213–25.

Gehan EA. The training of statisticians for cooperative clinical trials: a working statistician's viewpoint. *Biometrics* 1980; **36:** 699–706.

Hammond D. The training of clinical trails statisticians: a clinician's view. *Biometrics* 1980; **36:** 679–85.

. Julious SA, Pyke S, Hughes S. Best practice for statisticians in industry sponsored trials. *BMJ* 2011; 342: d1636.

Simon R. The role of statisticians in intervention trials. *Stat Methods Med Res* 1999; **8:** 281–86.

Partanen T. Do medical epidemiologists and statisticians really communicate? *Scand J Work Environ Health* 1999; **25:** 305–07.

Buderer NM, Plewa MC. Collaboration among emergency medicine physician researchers and statisticians: resources and attitudes. *Am J Emerg Med* 1999; **17:** 692–94.

Teo AR. The development of clinical research training: past history and current trends in the United States. *Acad Med* 2009; **84:** 433–38.

Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. New York: Springer, 2009.

Greenland S. Sensitivity analysis and bias analysis. In: Ahrens W, Pigeot I, eds. Handbook of Epidemiology, 2nd ed. New York: Springer, 2013.

Schulz KF, Grimes DA. The Lancet Handbook of Essential Concepts in Clinical Research. London: Elsevier, 2006.

Ley TJ, Rosenberg LE. The physician-scientist career pipeline in 2005: build it, and they will come. *JAMA* 2005; **294:** 1343–51.

Solomon SS, Tom SC, Pichert J, Wasserman D, Powers AC. Impact of medical student research in the development of physician-scientists. *J Investig Med* 2003; **51:** 149–56.

Marusić A, Marusić M. Teaching students how to read and write science: a mandatory course on scientific research and communication in medicine. *Acad Med* 2003; **78:** 1235–39.

Dorsch JL, Aiyer MK, Meyer LE. Impact of an evidence-based medicine curriculum on medical students' attitudes and skills. *J Med Libr Assoc* 2004; **92:** 397–406.

Houlden RL, Raja JB, Collier CP, Clark AF, Waugh JM. Medical students' perceptions of an undergraduate research elective. *Med Teach* 2004; **26:** 659–61.

Zier K, Friedman E, Smith L. Supportive programs increase medical students' research interest and productivity. *J Investig Med* 2006; **54:** 201–07.

Langhammer CG, Garg K, Neubauer JA, Rosenthal S, Kinzy TG. Medical student research exposure via a series of modular research programs. *J Investig Med* 2009; **57:** 11–17.

Moharari RS, Rahimi ER, Najafi A, Khashayar P, Khajavi MR, Meysamie AP. Teaching critical appraisal and statistics in anesthesia journal club. *QJM* 2009; **102:** 139–41.

Vujaklija A, Hren D, Sambunjak D, et al. Can teaching research methodology influence students' attitude toward science? Cohort study and nonrandomized trial in a single medical school. *J Investig Med* 2010; **58:** 282–86.

Glasziou PP, Sawicki PT, Prasad K, Montori VM, and the International Society for Evidence-Based Health Care. Not a medical course, but a life course. *Acad Med* 2011; **86:** e4.

Reproducibility practices and reward systems

Rennie D, Knoll E, Flanagin A. The international congress on peer review in biomedical publication. *JAMA* 1989; **261:** 749.

Bartneck C, Kokkelmans S. Detecting h-index manipulation through self-citation analysis. *Scientometrics* 2011; **87:** 85–98.

Kulkarni AV, Aziz B, Shams I, Busse JW. Author self-citation in the general medicine literature. *PLoS ONE* 2011; **6:** e20885.

Radicchi F, Fortunato S, Markines B, Vespignani A. Diffusion of scientific credits and the ranking of scientists. *Phys Rev E Stat Nonlin Soft Matter Phys* 2009; **80:** 056103.

Schreiber M. To share the fame in a fair way, hm modifies h for multi-authored manuscripts. *New J Phys* 2008; **10:** 040201-1–8.

Relating to Figure "Trends in six methodological quality indicators for publications of in-vivo studies "

Legend:
We randomly sampled 2000 records from PubMed (published 1960–2012) on the basis of their PubMed ID (See supplementary materials for details and for the study dataset). 254 publications described in vivo, ex vivo or in vitro experiments involving non-human animals. Two investigators independently judged whether the publication reported a sample size calculation, randomization, concealment of allocation sequence, blinded conduct of experiment, blinded assessment of outcome, or a conflict of interest statement. The proportion of studies reporting these is described in quintiles of publication year, along with their 95% confidence intervals. No study reported a sample size calculation, concealment of allocation sequence or blinded conduct of the experiment so these are not shown.
Protocol:
Study selection
Using the Rand(0) command in MS Excel we generated 2 sets of 1000 random numbers lying between 1 and 23,000,000. These were converted to a text format, and we used the find/replace function in MS Word to add the string "[PMID] OR " between each number, to give a text string "rand1[PMID] OR rand2[PMID] OR … OR randn[PMID]". This was then copied into the search field at www.pubmed.com and the search results retrieved as an xml file. Using Pubmed2XL this was converted to an MS Excel file, which was then imported to MS Access. We used an update query to add the term www.pubmed.com/ immediately prior to the pubmed id, and converted this to a hyperlink to allow the relevant PubMed page for that article to be accessed from within MS Access. We then deigned a data entry form to allow relevant publication characteristics to be added to the database.
Inclusion Criteria and data collection
In the first screen we determined whether a publication was a review article (including systematic reviews) or described primary research (including observational studies). We specifically excluded publications not in English, those exclusively in the fields of chemistry or physics, and descriptive reports, case reports, surveys, retrospective studies and correlation studies. We selected for further analysis publications describing experiments involving living biological non-human subjects either as whole live animals or as a source of experimental material (ex vivo or in vitro). Where a juvenile or embryonic form was studied in its natural environment we considered this to be in vivo,

whereas if it was removed to an artificial environment (eg xenopus oocytes for neurophysiology) we considered this to be in vitro.

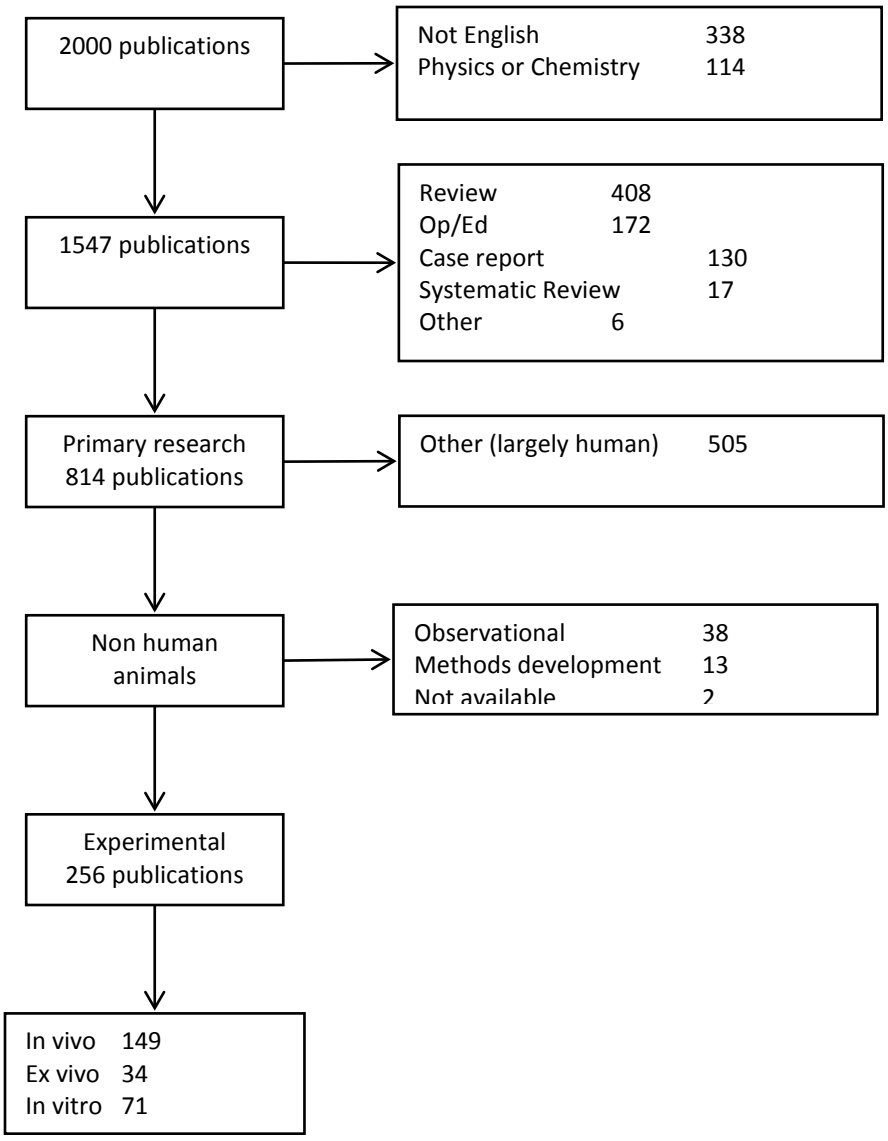
For remaining studies we retrieved the full text of the article and extracted data for the species of origin of the biological material; the research design (experimental or observational); the area of research; and whether the publication reported a sample size calculation, randomization, concealment of allocation sequence, blinded conduct of the experiment, blinded assessment of outcome, or a conflict of interest statement. Where a publication included multiple experiments we extracted data for in vivo experiments where these were presented, and where there were differences between experiments in the reporting of measures to reduce the risk of bias we scored the highest level of reporting. We scored reporting as being present, absent, or - where the use of a measure to reduce the risk of bias was not feasible, such as randomization for transgenic studies – as not applicable to that research design. Risk of bias items were scored independently by 2 observers each blinded to the assessment of the other, with differences resolved by discussion.

Data analysis

The data collected were entered into the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) data manager application in Microsoft Access 2003.

We assessed change in prevalence of reporting over time for each risk of bias item by calculating a proportion of studies reporting each measure to reduce the risk of bias, and its 95% confidence interval (using the Clopper-Pearson method in STATA).

Characteristics of included studies


2000 publications
Not English 338
Physics or Chemistry 114
1547 publications
Review 408
Op/Ed 172
Case report 130
Systematic Review 17
Other 6
Primary research
814 publications
Other (largely human) 505
Non human
animals
Observational 38
Methods development 13
Not available 2
Experimental
256 publications
In vivo 149
Ex vivo 34
In vitro 71