

Journal Watch

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SECTION EDITOR



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Are treatment effects significantly larger in trials published in a language other than English?

Annals of Internal Medicine published an excellent research article on the association between treatment effect estimates and publication characteristics.¹ Researchers from France and Germany (Academic hospitals and the Cochrane Centre) – and funded by Cochrane France – conducted the meta-epidemiologic study.

The objective was to compare treatment effects between published and unpublished randomised controlled trials (RCTs) and between trials published in English and other languages. They analysed 5659 RCTs included in 698 meta-analyses, and the study selection was well done, including data from Cochrane reviews published between March 2011 and January 2017, as well as trial references cited in the reviews. The study Included 356 unpublished trials and an additional 393 in a language other than English.

Treatment effects were larger in published trials rather than unpublished RCTs (combined ratio of odds ratios [ROR] for 174 meta-analysis, 0.90 with 95% CI, 0.82 to 0.98). Treatment effects were also larger for trials published in a language other than English. (combined ROR for 147 meta-analysis, 0.86 with 95% CI, 0.78 to 0.95).

These results confirm that restricting a search to published trials may lead to overestimation of treatment effects, possibly affecting meta-analysis results and conclusions. The study questions the recommendation to consider all languages in systematic reviews. There is language bias, as trials published in a language other than English showed larger treatment effect estimates than those published in English.

Are results of RCTs only published in English more reliable than RCTs in a non-English language?



Reference

1. Dechartres A, Atal I, Riveros C, Meerpohl J, Ravaud P. Association between publication characteristics and treatment effect

estimates: A meta-epidemiologic study. *Ann Intern Med.* 2018;169:385–93.

Certain European countries underperforming in cancer research relative to their GDP



A team of British researchers published a bibliometric analysis of European cancer research papers listed in the Web of Science index from 2002 to 2013 with the objective of quantifying research activity in 28 European Union (EU) member states, along with Iceland, Norway, and Switzerland (EU31). Data on disease burden were obtained from the World Health Organization. Papers were analysed by cancer anatomical and research domains. Sources of financial support (2009–2013) were searched. Country Gross Domestic Product (GDP) data

were used to contextualise the findings. There are limits to such a bibliometric search, which includes only published data, without appraising the quality of the research papers, nor the amount of funding per research paper. The main observations were:

- Cancer research papers from EU31 correlated well with national GDP ($r^2 = 0.94$).
- Certain cancer sites (lung, oesophagus, and pancreas) were under-researched relative to their increasing disease burden and poor prognosis.

- Central nervous system and blood cancers were more generously supported than their burden would warrant.
- Screening accounts for 8% of breast cancer papers, 1.7% of lung, 0.59% of oesophageal, and 0.33% of pancreatic research papers.
- An analysis of research domains indicated a paucity of research on radiotherapy (5%), palliative care (1.2%), and quality of life (0.5%).
- The European research portfolio needs to include more activity in surgery and radiotherapy, given their significant role in successful cancer treatment and control.
- There appears to be substantial support for two basic research domains, namely genetics and epidemiology. This focus may reflect the amount of publicity given to these domains in media stories.
- There is a particular need to encourage charitable and philanthropic funding in Eastern Europe, where cancer research support comes almost entirely from the central government.

Reference

1. Begum M, Lewison G, Lawler M, Sullivan R. Mapping the European cancer research landscape: An evidence base for national and Pan-European research and funding. *Eur J Cancer*. 2018;100:75-84.

Metawars: Meta-analyses were supposed to end scientific debates. Often, they only cause more controversy

Science recently published five papers on metaresearch, a scientific field of its own: “Research on research”, “Journals under the microscope”, “The metawars”, “A recipe for rigor”, and “Toward a more scientific science”.

Editors have created a new field called “journalology”. Metaresearchers have simple messages: Research practices should be questioned more, and if we understood better what we are doing, we might be able to do it better.

The metawars paper explores meta-analyses, as too many have conflicting results. In a meta-analysis, researchers collect all the evidence about a scientific question, weigh it impartially, and declare a “winner”.¹ There were about 11,000 new meta-analyses published in 2017, one-third of them by Chinese authors. This is a marked increase compared with

the fewer than 1000 published in 2000.

A good meta-analysis starts with clear criteria for study inclusion and exclusion. Scientists have to make several decisions and judgment calls that influence the outcome of a meta-analysis, mindful that anyone who wants to manipulate data has endless opportunities. Meta-analyses are popular because they can be done with little or no money, are publishable in high-impact journals, and, in turn, are often cited. Meta-analyses with conflicting conclusions become frequent, for example, in fields such as antidepressants, antiviral therapy for hepatitis C, flu treatments, associations between violence and games, and placebo effects.

Funding is a potential source of bias, but not the only one. Even if Cochrane meta-analyses are more rigorous than non-Cochrane meta-

analyses, that won't always eliminate conflict. Indeed, we recently observed a public dispute among Cochrane directors after the publication of a systematic review on HPV vaccine.² Resolving such conflicts is nearly impossible. Ideally, the future will see more transparency in opening up the data to allow colleagues to redo the meta-analysis... hoping that they will have no influence on the results.

References

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2. Jorgensen L, Gotzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evid Based Med*. 2018-111012.

Is cardiology research leading the way for achieving data sharing, compared to other medical specialties?



Data sharing in medicine lags behind that found in other scientific disciplines. The sharing of de-identified patient-level research data presents immense opportunities to all stakeholders involved in research. The cardiology team from the Yale School of Medicine described the efforts promoted by government, universities, sponsors, and industry players:

- Initiatives for data sharing and reporting of results come from several organisations: FDA (Food and Drug Administration), NIH (National Institutes of Health) and major funders (Bill & Melinda Gates Foundation, for example), PCORI (Patient-Centered Outcomes Research Institute), ICMJE (International Committee of Medical Journal

Editors), PRMA (Pharmaceutical Research and Manufacturers of America, and EFPIA (European Federation of Pharmaceutical Industries and Associations).

- Data-sharing platforms are numerous: government created platforms (NIH), industry-supported platforms such as Clinical Study Data Request, University and non-profit-based platforms such as the YODA Project.
- Many examples of data sharing experiences are described in this paper (SPRINT with the NEJM initiatives).
- The future of open data in cardiology will bring new incentives with researchers capitalising on the productivity of others

rather than creating original data. A “data authorship” system should be created. The sharing of clinical data by patients with researchers holds great potential, for example the NIH’s Sync for Science (S4S) programme.

- The revolution in data sharing that has transformed domains ranging from physics to genetics is just beginning for clinical medicine. Resolving the cost issue will be central to achieving a culture of sharing.

Reference

1. Dey P, Ross JS, Ritchie JD, Desai NR, Bhavnani SP, Krumholz HM. Data sharing and cardiology. Platforms and possibilities. *J Am Coll Cardiol.* 2017;70:3018-25.

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Analysis of two clinical trials registers – clinicaltrials.gov and EU Clinical Trials Register

Two different research teams from the UK analysed the reporting of results of clinical trials, with different objectives and methods.

US register: Results of industry-funded trials are more likely to be disclosed than those from other funders

All 45,620 clinical trials evaluating small molecules therapeutics, biological drugs, adjuvants, and vaccines completed after January 2006 and before July 2015 were included.¹ Among 27,835 completed efficacy trials (phase II-IV), 15,084 (54.2%) had disclosed their findings publicly. Industry was more likely than non-profit trial funders to disseminate trial results (59.3% versus 45.3%), and large drug companies had higher disclosure rates than small ones (66.7% versus 45.2%). Trials funded by the National Institutes of Health (NIH) were disseminated more often than those of other nonprofit institutions (60.0% versus 40.6%). Results of studies funded by large drug companies and

NIH were more likely to appear on clinicaltrials.gov than those from non-profit funders, which were published mainly as journal articles. Trials reporting the use of randomisation were more likely than non-randomised studies to be published in a journal article (34.9% versus 18.2%), and journal publication rates varied across disease areas, ranging from 42% for autoimmune diseases to 20% for oncology.

EU register: Compliance with the European Commission requirement for all trials to post results on the EUCTR within 12 months has been poor

The objective of this retrospective cohort study² was to ascertain compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) post results to the registry within 12 months of completion (final compliance date December 21, 2016); 7,274 of 11,531 trials listed as completed on EUCTR and where results could be established as due were included. Of 7,274 trials, 49.5% (95% confidence interval 48.4% to 50.7%) reported results. Trials with a commercial sponsor were substantially more likely to post results than those with a noncommercial sponsor (68.1% versus 11.0%, adjusted odds ratio 23.2, 95% confidence interval 19.2 to 28.2); as were trials by a sponsor who conducted a large number of trials (77.9% versus 18.4%, adjusted odds ratio 18.4, 15.3 to 22.1). More recent trials were more likely to report results (per year odds ratio 1.05, 95% confidence interval 1.03 to 1.07). Extensive evidence was found of errors, omissions, and contradictory entries in EUCTR data that prevented ascertainment of compliance for some trials.

References

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