Redefining the ‘E’ in EBM

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The philosopher of science, Thomas Kuhn, 1 would probably have called our reliance on biomedical journal trial evidence a paradigm. It has served us well, allowing the building of the philosophical 1 and practical 1 backbone of evidence-based healthcare. However, like all paradigms sooner or later it has begun to creak. Our reliance on journal articles needs a redefinition, if not a shift. In the last decade, 2 evidence has accumulated, 3 across a spectrum of different interventions, 4 that journal publications 5 cannot be trusted. Article reports of clinical trials suffer from a grave illness which is curable, but needs a concerted approach to prevent the growing threat of reporting bias. 5 When some of us started looking at the alternative sources of evidence for our Cochrane review of neuraminidase inhibitors 9 for influenza nearly a decade ago, we discovered that below every 10-page trial report lies a far deeper and more complex web of data and information needing attention. That is, if the trial was published in the first place.

The first problem is sheer bulk. For every page of journal article, there may be up to 8000 pages of regulatory data on the same clinical trial. 10 We call it a compression factor.

The next problem is bias. We reasoned that even the most faithful servant of evidence would not be able to publish a 10-pager based on a regulatory report without a radical selection of information and data. As we have no idea what the criteria for choosing which plum to publish are, this introduces unfathomable bias. Sometimes the bias is so bad that it distorts single trial reports, but it also distorts the findings of systematic reviews, as our neuraminidase inhibitor story shows. 9

Evidence of distortion in the results of research is now overwhelming, and it mainly comes from studies comparing journal articles with other sources of information. 11 These sources include register entries and different types of regulatory data now on offer, from regulators’ reports to clinical study reports (the regulatory equivalent of a journal publication), to overviews of whole trial programmes. Secreted and confidential up to a few years ago, clinical study reports are now coming to light from regulators and industry sources with seeming unstoppable momentum. Latest to look at releasing clinical study reports is the mighty Food and Drug Administration. 12 The catalyst to this change was the Nordic Cochrane Centre’s dogged insistence of access and the European Union Ombudsman’s support, 13 which ultimately led the European Medicines Agency to change its policies. 4 15

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inconsistencies\(^3\)). If there are distortions, they may be approved or overlooked by regulators.

Indexing, at least for now, is more resource-intensive than electronic database searches. The two can be run together and perhaps should be combined. But looking for regulatory data and compiling an index will give us a very good idea of what we are missing and what the limits of our reviews are. Ethics and Evidence both begin with ‘E’.

**Article translations**

There is a Spanish language translation of this article available as a data supplement.

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**Competing interests**

TJ was a corecipient of a UK National Institute for Health Research grant (HTA – 10/80/01 Update and amalgamation of two Cochrane reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children; https://www.journalslibrary.nihr.ac.uk/programmes/hta/108001#). TJ is also in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011–2014, TJ acted as an expert witness in a litigation case related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997–1999), GSK (2001–2002), Sanofi–Synthelabo (2003) and IMS Health (2013). In 2014–2016, TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. TJ has a potential financial conflict of interest on the drug oseltamivir. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. TJ had a potential financial conflict of interest on the drug oseltamivir. TJ was a signatory of a complaint to the European Ombudsman on maladministration in relation to the EMA investigation of possible harms from HPV vaccines. LJ has no competing interests to declare.

**Provenance and peer review**

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