Journal Watch

Journal Watch is based on the French-language blog *Rédaction Médicale et Scientifique*, by Hervé Maisonneuve available at http://www.redactionmedicale.fr.

SECTION EDITOR

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Publication record and time to publication: 85% of Pfizer-sponsored clinical trials were published in a peer-reviewed journal with a median time to publication of 31 months.

Treatment decisions made by healthcare professionals are informed by the results of clinical trials published in peer-reviewed journals. Research conducted on studies that were sponsored by the pharmaceutical industry and completed more than a decade ago highlighted issues of delayed, incomplete or biased publication of clinical trial results. For example, up to 57% of studies supporting approval of products by the US Food and Drug Administration (FDA) remained unpublished 5 years after product approval and those with favourable primary outcomes were more likely to be published. This retrospective, cross-sectional analysis included 76 clinical trials registered in ClinicalTrials.gov that completed in 2010 for approved, Pfizer prescription products in patients or vaccines in healthy participants. The primary outcome(s) for 65 (85%) studies was published in 71 manuscripts; the median time to publication was 31 months (range 3–63 months). Of the remaining 11 studies, two had been submitted to at least one journal, two had not yet been submitted and seven had no plans to publish because the study had terminated early due to recruitment challenges. Manuscripts accepted at the first choice journal were published at a median time of 28 months (range 8–63, n=31), those accepted at second choice journal were published at 32 months (3–45, n=19), and for those accepted at third choice journal, it was 40 months (range 24–53, n=13). The publication rate and median time to publication from study completion were comparable to those previously reported for combined analyses of industry and non-industry sectors. Opportunities exist for sponsors, authors and journals to explore ideas that would facilitate more timely publication for clinical trial results. However, to be effective, such changes may need to revisit the entire publication process.

Reference: Mooney LA, Fay L. Cross-sectional study of Pfizer-sponsored clinical trials: assessment of time to publication and publication history. BMJ Open 2016;6:e012362. doi:10.1136/bmjopen-2016-012362

To make replication studies more useful, researchers must make more of them, funders must encourage them and journals must publish them

Nature published a survey of 1,576 researchers who took a brief questionnaire on reproducibility research. More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments.

Most journals prefer to publish innovations, refusing to consider replication studies. A *Nature* proposes that researchers submit replications of experiements. Conventions around replication are in their infancy – even the vocabulary is inadequate. Nowadays, researchers who want to tell the scientific community about their replication studies have multiple ways to do so. They can chronicle their attempts on a blog, post on a preprint server or publish peer-reviewed work in those journals that do not require novelty. The editorial lists journals that have a column dedicated to replication studies.

Nature concludes: *'To foster better behaviour, replication attempts must become more common. We urge researchers to open their file drawers. We urge authors to cooperate with reasonable requests for primary data, to assume good intent and to write papers – and keep records — assuming that others will want to replicate their work. We urge funders and publishers to support tools that help researchers to thread the literature together. We welcome, and will be glad to help disseminate, results that explore the validity of key publications, including our own'.*

References:

Baker M. 1,500 scientists lift the lid on reproducibility. Nature 2016;533:452-4.

Go forth and relicate [editorial]. Nature 2016;536:373.2016;536:373.

The family wasn't aware that playing bagpipes was the cause of the death: consent for publishing patients' data is mandatory

Family members learned a bagpipe musician died from inhaling mould and fungi from a case study reported in *Thorax*. The family was told he had a fatal condition called pulmonary fibrosis and a heart condition had caused his death. The family's distress was extensively covered by the UK's mainstream media. The hospital has apologised; the journal, however, did not issue a retraction. The Thorax paper says the patient gave consent, and according to the co-editor-in-chief of the journal, consent was sought from the family. But the patient's daughter told RetractionWatch that neither the next of kin nor the patient were approached for consent.

This observation reminds us that obtaining signed consent from patients is mandatory to publish any case report. This is not the first case report to cause distress to the family of the deceased.

Reference: Chawla DS. Despite apology, bagpipes study not slated for retraction. 2016 [cited 9 Oct 2016]. http://retractionwatch.com/2016/09/07/despite-apology-bagpipes-study-not-slated-for-retraction/

Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired.

This 30 pages paper was based upon a talk given at the Cochrane Colloquium in Vienna, October 2015, by JPA Ioannidis, director of the Meta-Research Innovation Center at Stanford (METRICS). The production of systematic reviews and meta-analyses has reached epidemic proportions. Currently, there is massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses. Instead of promoting evidence-based medicine and health care, these instruments often serve mostly as easily produced publishable units or marketing tools. A total of 9,135 meta-analyses were published and 28,959 systematic reviews were indexed in PubMed in 2014, which is more than articles on new randomised trials. It is debatable whether systematic methods for searching and integrating evidence has been followed in generating all of these reviews. China has rapidly become the most prolific producer of English-language, PubMed-indexed meta-analyses. The most massive presence of Chinese meta-analyses is on genetic associations (63% of global production in 2014), where almost all results are misleading since they combine fragmented information from mostly abandoned era of candidate genes. Many contracting companies working on evidence synthesis receive industry contracts to produce meta-analyses, many of which probably remain unpublished.

Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired. The publication of systematic reviews and meta-analyses should be realigned to remove biases and vested interests and to integrate them better with the primary production of evidence

Reference: Ioannidis JPA. The mass production of redundant, misleading and conflicted systematic reviews and meta-analysis. Milbank Q 2016;94:485-514.

Systematic reviews of drugs might be improved by including protocols and clinical study reports in addition to published articles

Little is known about how adverse events (AEs) are collected and reported in clinical trials. Gøtzsche *et al.* (Nordic Cochrane Centre) analysed seven randomiwed placebo-controlled trials (4,225 participants) conducted between 1992 and 1996 in the US and Europe, on orlistat, an anti-obesity drug that was approved by the European Medicine Agency in 1998. In 2011, the FDA issued a warning regarding 13 cases of liver failure associated with orlistat. The authors identified important disparities in the reporting of AEs between protocols, clinical study reports (CSRs), and published papers. Reports of these trials seemed to have systematically understated the AEs. None of the protocols or CSRs contained instructions for investigators on how to question participants about AEs. All AEs were coded by the sponsor using a glossary that could be updated by the sponsor. Between 3% and 33% of the total number of investigator-reported AEs from the

The SAGER guidelines encourage a more systematic approach to the reporting of sex and gender in research across disciplines

Sex and gender differences are often overlooked in research design, study implementation and scientific reporting, as well as in general science communication. This oversight limits the generalisability of research findings and their applicability to clinical practice, in particular for women but also for men. The Sex and Gender Equity in Research (SAGER) guidelines are a comprehensive procedure for reporting of sex and gender information in study design, data analyses, results and interpretation of findings. The SAGER guidelines are designed primarily to guide authors in preparing their manuscripts, but they are also useful for editors, as gatekeepers of science, to integrate assessment of sex and gender into all manuscripts as an integral part of the editorial process.

The SAGER guidelines are the result of collective effort by the EASE (European Association of Science Editors) Gender Policy Committee. A panel of 13 experts representing nine countries developed the guidelines through a series of teleconferences, conference presentations and a 2-day workshop. An internet survey of 716 journal editors, scientists and other members of the international publishing community was conducted as well as a literature search on sex and gender policies in scientific publishing.

Sex refers to a set of biological attributes in humans and animals that are associated with physical and physiological features such as chromosomes, gene expression, hormone function and reproductive/sexual anatomy. Gender refers to the socially constructed roles, behaviours and identities of female, male and gender-diverse people.

The underrepresentation of women in research can result in adverse consequences. Among the ten prescription pharmaceuticals withdrawn from the US market between 1997 and 2001, eight caused greater harm to women than men. More recently, the FDA issued a safety communication, recommending half a dose of zolpidem for women, due to greater susceptibility to the risks of the drug. It is acknowledged that many studies are not "designed" to analyse sex and/or gender differences.

As a general principle, the SAGER guidelines recommend careful use of the words sex and gender in order to avoid confusing both terms. The term sex should be used as a classification of male or female based on biological distinction to the extent that this is possible to confirm. In animal studies, the term sex should be used. In cell biological, molecular biological or biochemical experiments, the origin and sex chromosome constitutions of cells or tissue cultures should be stated. In other disciplines, such as the testing of devices or technology on humans, authors should explain whether it will be applied or used by all genders and if it has been tested with a user's gender in mind.

The SAGER guidelines are summarised in Table 1.

Table 1. Sex and Gender Equity in Research (SAGER) guidelines

General principles

- Authors should use the terms sex and gender carefully in order to avoid confusing both terms.
- Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected.
- Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction

Recommendations per section of the article

Title and abstract	If only one sex is included in the study, or if the results of the study are to be applied to only one sex or gender, the title and the abstract should specify the sex of animals or any cells, tissues and other material derived from these and the sex and gender of human participants.
Introduction	Authors should report, where relevant, whether sex and/or gender differences may be expected.
Methods	Authors should report how sex and gender were taken into account in the design of the study, whether they ensured adequate representation of males and females, and justify the reasons for any exclusion of males or females.
Results	Where appropriate, data should be routinely presented disaggregated by sex and gender. Sex- and gender-based analyses should be reported regardless of positive or negative outcome. In clinical trials, data on withdrawals and dropouts should also be reported disaggregated by sex.
Discussion	The potential implications of sex and gender on the study results and analyses should be discussed. If a sex and gender analysis was not conducted, the rationale should be given. Authors should further discuss the implications of the lack of such analysis on the interpretation of the results.

Reference: Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Res Integrity Peer Rev (2016) 1:2.

trials were reported in the publications because of post-hoc filters, though six of seven papers stated that "all AEs were recorded."

In one trial, the majority of patients had multiple episodes of the same AE that were only counted once, though this was not described in the CSR. Participants treated with orlistat experienced twice as many days with AEs as participants treated with placebo (22.7 d versus 14.9 d, p-value <0.0001, Student's *t* test). Furthermore, compared with the placebo group, AEs in the orlistat group were more severe. None of this was stated in the CSR or in the published paper.

This was an explorative study, restricted to one drug tested in the mid-1990s; therefore, the results might not be applicable for newer drugs as the standards of reporting CSRs and publications have improved since. However, many drugs approved in this time period are currently in the market. The authors highlight the need for detailed analysis plans for harms data.

Reference: Schroll JB, Penninga E, Gøtzsche P. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of orlistat: a document analysis. PLOS Med 2016;13(8):e1002101.