# Hayashi's problem
# The use of regulatory information for research synthesis

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A recent survey has shown that only 10% of Cochrane reviews make serious efforts to search for and include unpublished material. The recent series of cases of exposure of sponsor bias changing our understanding (and is some cases the registration) of important interventions (second generation antipsychotics, rosiglitazione, riboxetine, vioxx, tamiflu) has shown that reliance on published material can be highly misleading. Journals (and ultimately research synthetisers and decision-makers) are usually presented with a very short summary of a selected trial which is part of a larger research programme. Given the growing realization that these form a potentially biased evidence base, we may need to develop explicit methods for including regulatory material in systematic reviews or require producers to make all material available to journals (an unrealistic option). First however we need to know this is feasible and worthwhile. Tom Jefferson will present and discuss some of these issue on the basis of the oseltamivir (Tamiflu) review, starting with the story of how his team realized their previous Cochrane review on Tamiflu were biased and how they went about addressing the issue.

"Our 2006 neuraminidase inhibitors (NI) for influenza Cochrane review was misleading. Its optimistic findings were wholly based on a mixture of published and glimpses of unpublished material taken at face value without adequate critical appraisal. Efforts to ascertain the presence or extent of publication bias were not in depth. Subsequent versions of the review have revealed the existence of considerable reporting bias. Industry has no obligation to publish all its trials, but are bound to disclose them to regulators when seeking registration. Thanks to UK NIHR funding, we are at present updating our NI review by looking only at unpublished data to minimise the risk of any type of reporting bias. Our current review includes both internal pharma trial reports which are 200-300 fold larger than their published counterparts and regulatory files. These are either currently available of requested through FOIA rules from the FDA, UK NICE, EMA and Japanese PMDA. So far regulatory material (in the guise of new drug application appraisal reports) has proved invaluable in integrating internal trials reports and providing additional information for their critical interpretation."

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**Main related publications:**


Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006;367:303-13.

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Doshi P, Jones MA, Jefferson T. Rethinking credible evidence synthesis. BMJ 2012;344:d7898 doi: 10.1136/bmj.d7898.

Drug Data Shouldn't Be Secret by Peter Doshi and Tom Jefferson
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Tamiflu open data campaign
http://www.bmj.com/tamiflu

Also:

Editorial
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Correspondence
Godlee F. Open letter to Roche about oseltamivir trial data*BMJ* 2012;345:e7305 doi: 10.1136/bmj.e7305 (Published 29 October 2012).
http://www.bmj.com/content/345/bmj.e7305

Podcast (click on the fish icon right hand side, upper corner of webpage)
http://www.bmj.com/multimedia

http://www.nytimes.com/2012/11/01/business/british-medical-journal-to-require-detailed-clinical-trial-data.html?_r=0

Watch Tom Jefferson relate the story on: http://www.youtube.com/watch?v=pTrqsif0KWM

http://blog.okfn.org/2012/11/19/the-tamiflu-story-why-we-need-access-to-all-data-from-clinical-trials/