Interim guidance on how to decide whether to include clinical study reports and other regulatory documents into Cochrane reviews

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Trusted evidence.
Informed decisions.
Better health.
TJ was a co-recipient of a UK NIHR grant (HTA – 10/80/01 Update and amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children: [http://www.nets.nihr.ac.uk/projects/hta/108001](http://www.nets.nihr.ac.uk/projects/hta/108001)). TJ receives royalties from Blackwells and Il Pensiero Scientifico Editore, Rome. TJ is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013, TJ acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997-99 TJ acted as a consultant for Roche, in 2001-2 for GSK, and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral, which did not get approval from the Food and Drug Administration). TJ was a consultant for IMS Health in 2013, and in 2014 was retained as a scientific adviser to a legal team acting on the drug Tamiflu (oseltamivir, Roche). In 2014-15 TJ was a member of two advisory boards for Boehringer and is in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ has a potential financial conflict of interest in the investigation of the drug oseltamivir. TJ is acting as an expert witness in a legal case involving the drug oseltamivir (Roche). TJ is a member of an Independent Data Monitoring Committee for a Sanofi Pasteur clinical trial.
Past. I received €1500 from the European Respiratory Society in support of my travel to the society’s September 2012 annual congress in Vienna, where I gave an invited talk on oseltamivir. Between 2011-2014, I was a co-recipient of a UK National Institute for Health Research grant to carry out a Cochrane review of neuraminidase inhibitors (PI: Carl Heneghan). In 2015, I received $11,000 from the American Association of Colleges of Pharmacy to fund a PhD student to assist me in studying consumer medical information about the possible harms of statins. Between 2014-2016, I was on a PCORI funded grant to compare data from multiple sources (ME-1303-5785; PI: Kay Dickersin), and from 2015-2018, on a Cochrane funded Methods Innovation Fund grant to develop guidance regarding when to use regulatory data in Cochrane reviews (PI: Tom Jefferson).

Present. From 2017 to 2020, the Laura and John Arnold Foundation has funded me to run a RIAT Support Center (PI: Doshi).

Summary
• Public, foundation, and non-profit funding of academic research
• Reimbursement (e.g. lodging, travel) from non-profits
• No industry funding
Context

• Increasing evidence of reporting bias in reports of clinical trials published in the biomedical literature

• Increasing availability of “regulatory documents” from a variety of sources, triggered by the NCC stance
  – EMA Policy 0043 & 0070; also, ClinicalStudyDataRequest.com, YODA, etc.

• First Cochrane review published in 2014 based wholly on regulatory documents (Tamiflu)

• “Regulatory documents” can provide thousands of pages more for each trial published page, when published
Cochrane MIF funded Project

**Process & products**

8 strong multidisciplinary team of Cochrane authors and methodologists

2-phase survey of authors

Presentation & seminars at 2 Colloquia (Vienna, Seoul)

Peer review

Cochrane-wide consultation

Interim guidance – with proposals for use of regulatory data especially in reviews of high value or with evidence of reporting bias, or both

Recommendation: investment in infrastructure needed
**Additional product: glossary**

- **Biologic License Application (BLA).** The regulatory vehicle through which sponsors submit a biologic for possible marketing approval to the **Food and Drug Administration.** The requirements are similar, but not identical, to those of a **New Drug Application.**

- **Blank Case Report Form.** A sample **Case Report Form (CRF),** of unique pages only, that is, empty forms not yet filled in. One copy of all CRFs used in a trial is typically contained in section 16.1.2 of **Clinical Study Reports** formatted according to the **ICH E3 guidelines.**
  - Example: *Tamiflu (oseltamivir) trial NV18671 PDF page 336-527*
  - Also see an example in the Screenshots Gallery

- **Case Report Form (CRF).** The original paper or electronic forms on which individual participants’ data (demographic, efficacy, safety, etc) are recorded during the clinical trial. The forms are typically the most ‘raw’ form of detailed data available for understanding what happened in a clinical trial, and the data they contain are statistically analysed only after they have been entered into an electronic database of individual patient data. Forms can vary in length, from a few pages to hundreds of pages, and each trial can have multiple forms—for example, for different visits or for the different tests or procedures the participant undergoes.
  - Example: *Arthronat trial MA-CT-10-002 PDF pp. 3985-4749.*
  - Also see an example in the Screenshots Gallery
Certificate of analysis (Source: Tamiflu (Oseltamivir) trial WP16263 PDF pp. 422-3)

Tamiflu™ (oseltamivir phosphate) Clinical Study Report

Protocol WP16263 Research Report 1003328

Placebo Capsules
Ro 84-0796/V16

CERTIFICATE OF ANALYSIS

No. 07039556
Batch: G MZ 0163

Date of manufacture: August 1999
Batch size: 104’827 capsules
Place of manufacture: Hoffmann-La Roche Ltd, Basle, Switzerland
Date of analysis: September 1999
Retest date: 08.2002

Capsule size
No. 2

Colour of the capsules
Grey, opaque
Ivory, opaque

Capsule contents
Powder
White

Identity of
Ro 84-0796
Dethydrocholic acid

Quality Control & Assurance
Basel, Switzerland

Draft 09/30/1999
Ro-84-0796.Cap.V16.05.2.2,16.07.039556
Glossary with Screenshots
Limitations

Limited scope (for now) to:
- «When» not «How»
- Regulated pharmaceuticals

Potentially time consuming

So far, only 4 SRs allowing assessment of gain from regulatory data over publications; all show differences in conclusions (influenza antivirals, rhBMP-2 (two SRs), and reboxetine)
Strengths

Inclusion of CSRs and other regulatory documents provide the best current chance to minimise the effects of known and unknown reporting biases on our reviews

Steals a march and keeps Cochrane cutting edge

Evidence and Ethics
Questions?