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Risk of bias in industry-funded oseltamivir trials: comparison of journal publications and unpublished clinical study reports

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Abstract

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Background

The Cochrane risk of bias tool is a prominent instrument used to evaluate potential biases in clinical trials. In three updates of our Cochrane review on neuraminidase inhibitors, we assessed risk of bias on the same trials using different levels of detail: the trials in journal publications, in core reports, and in full clinical study reports. Here we analyze whether progressively greater amounts of information and detail in clinical study reports (including trial protocols, statistical analysis plans, certificates of analyses, individual participant data listings and randomization lists affected our risk of bias assessments.

Methods and Findings

We used and extended the Cochrane risk of bias tool to assess and compare risk of bias in 14 oseltamivir trials (reported in 10 clinical study reports) obtained from the European Medicines Agency (EMA) and its manufacturer, Roche. With more detailed information, no previous assessment of “high” risk of bias was reclassified as “low” or “unclear”, and over half (55%, 34/62) of previous assessments of “low” risk of bias were reclassified as “high”. Most “unclear” risk of bias (67%, or 28/42) was reclassified as “high” risk of bias when our judgments were based on full clinical study reports. Limits of our study were our relative inexperience in dealing with large information sets, sometimes subjective bias judgments and focus on industry trials. Comparison with journal publications was not possible because of publication bias the limits of the Cochrane tool.

Conclusions

The current Cochrane risk of bias tool is primarily designed to aid the critical evaluation of trials published in journal publications, but full clinical study reports allow for bias to be actually measured rather than reported as an un-quantified risk. Further development may be necessary.

Strengths and limitations of this study

- The availability of full clinical study reports decreased the uncertainty of biases and allowed definitive judgments to be made
- The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text.
- Our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents may limit our findings
- The current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information that are found in clinical study reports.
- The instrument we have developed is for use with clinical study reports, and may not apply to non-industry trials

Introduction

The risk of bias tool in Cochrane reviews of randomized trials is routinely used to assess standard items considered critical to trial study design such as random sequence generation, allocation concealment, attrition and performance biases. There are six standard bias elements, each rated as either at "high", "low", or "unclear" risk of bias.

As Cochrane reviews are mostly based on synthesizing studies based on reports published in the scientific literature, the risk of bias tool is traditionally applied to journal publications. To our knowledge, how risk of bias judgments may change when they are based on more detailed reports of trials such as clinical study reports has not been previously investigated.

Clinical study reports are considered the most exhaustive summaries of randomized controlled trials of pharmaceuticals. Clinical study reports are highly structured and detailed documents that follow an outline format agreed between regulators and manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency policies adopted by the European Medicines Agency,[3] as well as recent announcements by some pharmaceutical companies to make clinical study reports more readily available [4,5] suggest that clinical study reports may increasingly be incorporated into systematic reviews and other forms of evidence synthesis.

Although there is some variation in the structure and content of clinical study reports, they are usually composed of a main report of the trial (sections 1-15 of the ICH E3 document, called a “core report” in oseltamivir clinical study reports). A core report is structured in Introduction, Methods Results and Discussion (IMRAD) style that is accompanied by numerous appendices, which contain important supplementary data needed to understand and interpret the trial, its context and history (section 16 of ICH E3). [1,2] These appendices include such documents as the trial protocol, protocol amendments, statistical analysis plan, blank case report forms, certificates of analysis, randomization list, and informed consent form. For the purposes of this paper the core report plus all its appendices (roughly equivalent to modules II to V in oseltamivir clinical study reports) will be known as the full clinical study report.

Such documents theoretically can help reduce uncertainty in judging risk of bias.

In 2012, we published an update of our Cochrane review of neuraminidase inhibitors for which a total of 32 oseltamivir trials were eligible. Unlike most Cochrane reviews, this review was based only on clinical study reports but because of the lateness of delivery of clinical study reports and our funding timelines, the review update was based only on core reports. [6] Risk of bias assessments were therefore based on the each clinical study report’s core report. Subsequently in 2013, we obtained full clinical study reports from Roche, and as part of a further systematic review update, carried out new risk of bias assessments of the same trials based on the full clinical study reports.

We aimed to investigate whether and how the level of detail in reporting a trial affects judgments about risk of bias, by comparing reports of the same trial with widely varying

level of detail. These were journal publications, core reports, and full clinical study reports. As well as using the standard Cochrane risk of bias tool, we developed an additional list of study elements we wanted to extract to help us better judge each trial's design and conduct and help us in the task of organizing large quantities of information now available to us.

In this report we describe our use of these tools to address three specific questions:

1. Do core reports change the risk of bias evaluation compared to published papers?
2. Do full clinical study reports change the risk of bias evaluation compared to core reports?
3. Do full clinical study reports change the risk of bias evaluation compared to published papers?

In summary we intended to analyze whether progressively greater amounts of information and detail in clinical study reports (including trial protocols, statistical analysis plans, certificate of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments

Methods

Core reports for 14 trials contained in 10 Clinical study reports (M76001; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978; NV16871) were received from Roche and EMA by 12 April 2011 (the date of time-lock for our Cochrane review).[6] The current Cochrane risk of bias tool was first introduced in 2010. The tool consists of six domains, each may have more than one source of bias application, depending on the subject matter.[7] Our applications were as follows: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel – all outcomes), detection bias (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms, complications and harms outcome data), reporting bias (selective reporting) and other bias. The identification of sources of other bias was left at the reviewers' discretion.

The reporting of more than one trial in the same clinical study report is unusual. Roche gave low influenza circulation and the consequent need to pool studies as the reason. Trial risk of bias assessments were performed following Cochrane methods [7] and published in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis of data extracted from core reports. Risk of bias assessments were re-extracted from the 2012 review for this study.

In April 2011, we began to obtain the appendices of the clinical study reports included in our review. For most clinical study reports we requested, EMA had the protocol, protocol amendments, statistical analysis plan, blank case report forms, and other appendices contained in what Roche terms the second "module" of a full clinical study report (see Appendix 1). However EMA did not possess—and therefore could not provide us with—full clinical study reports with the exception of trial WP16263.[8] For approximately three years Roche had repeatedly refused our requests for full clinical study reports.[9]

In the course of carrying out these new extractions, Roche changed its policy on access to data and pledged in April 2013 to share with us 77 full clinical study reports (www.bmj.com/tamiflu/roche). Twenty trials were included in the analysis of our current reviews.[10] As we were already in possession of core reports and appendices such as the protocol and statistical analysis plan for the 14 trials in this analysis, the additional data for other clinical study reports provided by Roche does not concern this paper. In the Clinical study reports Roche redacted information that they judged to be of “legitimate commercial interest” or present a risk of trial participant re-identification. For our purposes, the redactions did not impede an analysis of risk of bias.

Based on our growing familiarity with clinical study reports, we designed and piloted an extraction sheet to record how our understanding of the trials changed in light of availability of the additional appendices. We realized that in addition to the standard Cochrane risk of bias elements, we needed to organize the abundant material at our disposal and re-construct a timeline of the trials. We added the following elements to our extraction sheets: date of participant enrollment, unblinding of the trial, protocol for which we had the full text, protocol amendments, statistical analysis plan for which we have the full text (and its amendments), patient consent form, randomization list, and certificate of analysis. The finalized extraction sheet is in Appendix 2.

Based on access to full clinical study reports, we carried out our final assessment of risk of bias. These were carried out by a single reviewer, checked by a second with final consensus reached through a face-to-face discussion among the entire group.

Because with full clinical study reports there should be no ambiguity, we only allowed "low" or "high" risk of bias judgments (i.e. no “unclear”). We adopted the position that, unlike a publication which may have page limits, there was no reason a full clinical study report should be missing details necessary for a third party to judge risk of bias. Therefore, when information that would have otherwise allowed us to judge a risk of bias as either "low" or "high" was missing, this would automatically be categorized as “high” risk of bias. This decision to eliminate the “unclear” option when assessing full clinical study reports was made following an initial assessment of the trials, which included “unclear” judgments. One peer-reviewer of this paper suggested we analyze the data had we kept the “unclear” judgment, so we also carried out this post-hoc analysis.

To allow for a comparison of risk of bias judgments based on published reports of trials and risk of bias judgments based on clinical study reports (either core reports alone or full clinical study reports), we used our previous risk of bias judgments for the same trials in the relevant Cochrane reviews that had been based on publications.[11,12]

The extraction and adjudication methods used were the same as those used in our subsequent unified Cochrane review.[6]

We used descriptive methods to answer our three questions without the need for formal statistical analysis.

Ethics approval and patient consent forms are not provided as they are not necessary for a Cochrane review, of which this study is a product.

Results

We could only compare risk of bias assessments where we had a record of risk of bias assessments that were based on, firstly, core reports alone, and then, full clinical study reports. We had these for the following 14 trials (reported in 10 clinical study reports): WV15730, WV15707, M76001, WV15812 WV15872, WV15819/WV15876/WV15978, WV15670, WV15671, NV16871, WV15759/WV15871, WV15799.

We could not carry out a comparison of risk of bias judgments of journal publications with core reports or full clinical study reports because our assessments were largely based on secondary and not primary publications of the trials and an outdated risk of bias tool. There were therefore too few studies for which we had distinct risk of bias judgments of primary journal publications (many studies for which we have clinically study reports were and remain unpublished). In addition, the current Cochrane risk of bias tool was introduced after the production of our review based on published articles, making the comparison, had we had the data to undertake it, more difficult to interpret and possibly unfair. For the comparison of core and complete clinical study reports, Table 1 shows that no previous assessment of “high” risk of bias was reclassified as “low” or “unclear” in the presence of more detailed information. Previous assessments of “low” risk of bias were not uncommonly reclassified as “high” bias in the subsequent assessment. While our assessments based on core reports were mostly classified as “low risk of bias” they were reclassified in the opposite direction as “high” risk of bias when our judgments were based on full clinical study reports (Table 1).

Had we kept the “unclear” risk of bias judgment option when assessing full clinical study reports [10] we would have had 64 “unclear” judgments. The breakdown of these 64 into the various attributes is:

- Attrition bias: symptoms (10); complications (9); safety (15). These were unclear because we do not know the impact of missing symptoms data, the reports contained unclear definitions for secondary complications of influenza, and a seemingly problematic decision tool for the alternative designation of events as either complications or harms, which we called “compliharms” in our Cochrane review.
- Other bias (13) – these are unclear due to the unknown effect of the de-hydrochloric acid included in the placebo but not included in the active treatment
- Performance bias (6) – these are unclear due to missing certificates of analysis describing the placebo appearance
- Selection bias (10) – these are unclear due to the missing or unclear randomisation lists meaning we cannot confirm random sequence generation
- Detection bias (1) – unclear due to unknown impact of different coloured placebo caps on outcome assessment

See Tables 2 and 3. Twenty nine percent of previously certain judgments (“high” or “low” risk of bias) based on core reports became “unclear” with full clinical study reports.

An example of the kind of detail available in full clinical study reports and the importance of the trial timeline in assessing presence of bias is the observation that of the clinical study reports for the 14 trials, only 1 contained a protocol which predated the beginning of participant enrolment, only 2 had statistical analysis plans which clearly predated participants enrolment and 3 had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding.

Completed extraction sheets with risk of bias comparisons and rationales are available on request from the corresponding author.

Discussion

We used the Cochrane six-item risk of bias instrument to assess bias under two different levels of detail in trial reporting. The availability of full clinical study reports decreased the uncertainty and allowed definitive judgments to be made. “Unclear” risk of bias became a more certain "low" or "high" risk of bias, or even certainty of bias. Certainty or low levels of uncertainty were recorded against instances where our expectations of having all relevant and consistent information available for our reviews. When the information was not available, our judgments changed because we found gaps in the availability of information and inconsistent information. Whether the full study reports represent an exhaustive and coherent source of trial narrative and data remains unclear.

Throughout our study we were assessing two different types of material within the clinical study reports: those that were created or written prior to patient enrollment (e.g. trial protocols), and those written after (e.g. core reports).

This approach is not possible when assessing trials reported in journal publications, in which articles necessarily reflect post hoc reporting at a far more sparse level of detail. We suggest that when bias is so limiting as to make meta-analysis results unreliable, it either should not be done or a prominent explanation of its clear limitations should be posted alongside the meta-analysis. We found the Cochrane risk of bias tool to be difficult to apply to clinical study reports. We think this is not because the tool was constructed to assess journal publications but as with all list-like instruments its use lends itself to a check-list approach in which each design item is sought and if found eliminated from the bias equation. Similarly, the instrument we assembled needs to be applied with thought and consideration – an approach that does not lend itself to reviewing under time pressure. However more focus should be devoted to bias itself and its effects rather than theoretical *risk* of bias. Many of the variables we found to be important when assessing the trial (e.g. date of trial protocol, date of unblinding, date of participant enrollment) are simply not captured in the risk of bias tool when used in a routine way or to review publications. We were also often unsure how to judge the risk of bias when bias itself can actually or potentially be measured given the detailed data available in full clinical study reports. If, for example, detailed information about participants that withdrew from the trial is available, one can judge whether this attrition created an actual bias or not. In such a

situation, it seems to make little sense to judge the risk (i.e. potential) of attrition bias, but this is what the Cochrane tool asks us to do.

Box 1 shows examples of the types of information found in clinical study reports that led to risk of bias assessment changes. While the judgments of "low" or "high" risk of bias may portray certainty, particularly when based on the reading of a full clinical study report, we found ourselves often in lengthy debate and discussion over the proper level of risk of bias before arriving at a consensus. We found the risk of bias judgments themselves to carry a great amount of subjectivity, in which different judgments can be justified in different ways. The real strength of the risk of bias tool appears not to be in the final judgments it enables, but rather in the process it helps facilitate: critical assessment of a clinical trial.

Another aspect that became obvious is that tools based on publications are designed to detect presence, absence or uncertainty regarding elements in a very restricted number of places in the text. The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text. An example of this active engagement is the cross-checking of active principle and placebo batches used across trials and their connection with a visual description of their properties such as color in a certificate of analysis. For example, once the presence of a differently colored placebo capsule cap in trial WP16263 was identified through the clinical study report's certificate of analysis, its potential impact on blinding was captured in the Cochrane instrument. The interpretation of such a finding is open to question, as the colors of the active principle and placebo capsule caps are close (ivory and light yellow). However publication-based or core report only based assessments would not have identified the potential differences in color as the descriptions given are "placebo" [13] and "matching placebo" [14] respectively.

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents such as randomization lists. Randomization lists appeared to be of two types. The first was a pre-randomization list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post-hoc randomization list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not provided or original codes cannot be matched to patients. Another limitation of our study is the instrument we have developed is for using with clinical study reports, and may not apply to non-industry trials (which may not have a clinical study report).

As evidence of reporting bias in industry trial publication mounts, [8,15–20] we believe Cochrane reviews should increasingly rely on clinical study reports as the basic unit of analysis. The systematic evaluation of bias or risk of bias remains an essential aspect of evidence synthesis, as it forces reviewers to critically examine trials. However, the current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information that are found in clinical study reports. Until a more appropriate instrument is

developed, we propose our tool as a possible interim measure to be used and adapted across a wide range of clinical study reports.

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Contributorship statement. All author fulfils all three of the ICMJE guidelines for authorship which are '1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.' If anyone currently listed as an author doesn't fulfil all three of these then they should be moved to the acknowledgment section.

Financial Disclosures

Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as 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 FDA).

Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir.

Dr Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and receives fees for editorial and guideline developmental work and royalties from books and

in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled “Tamiflu: harmful as was afraid” and “In order to escape from drug-induced encephalopathy”. Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

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Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 [cited 2012 Jul 8]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

2. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open. 2013 Feb 26;3(2):e002496.

3. European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043 [Internet]. 2010 [cited 2012 May 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf

4. F. Hoffmann-La Roche Ltd. Roche Global Policy on Sharing of Clinical Trials Data [Internet]. 2013 [cited 2013 Jun 19]. Available from: http://roche-trials.com/dataSharingPolicy.action

5. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. N Engl J Med. 2013;369(5):475–8.

6. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;(1):CD008965.

7. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

8. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. BMJ. 2012 Jan 17;344:d7898.

9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med. 2012 Apr 10;9(4):e1001201.

10. (Last) (First). This is a placeholder reference for an unpublished manuscript. It will be populated when publication information is available.

11. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744.

12. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2010;2:CD001265.

13. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 May;35(5):461–7.

14. Hoffman-La Roche, Ltd. Clinical Study Report – Protocol WP16263. A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Report No. 1003328. 2001.

15. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.

16. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963–71.

17. Vedula SS, Li T, Dickersin K. Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-Label Uses of Gabapentin. PLoS Med. 2013 Jan 29;10(1):e1001378.

18. Rodgers MA, Brown JVE, Heirs MK, Higgins JPT, Mannion RJ, Simmonds MC, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ. 2013;346:f3981.

19. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341(oct12 1):c4737–c4737.

20. Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med. 2013 Oct 8;10(10):e1001526.

Box 1: Examples of risk of bias assessment changes and other concerns

- In trial WV15708, the risk of bias related to allocation concealment went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because the full clinical study report did not report sufficient details about the method of allocation concealment.
- In trial WV15707, the risk of bias related to random sequence generation went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because a full description of the randomization procedure was not provided.
- Prophylaxis trials WV15673 and WV15697 are described as "identical" but this could not be verified as we only had one protocol (and the protocol we did have was dated after study completion). In addition, the placebo event rates for influenza infection were very different between the two trials and their pooling, combined with the redaction of center numbers, preventing from being individually added to a meta-analysis. Therefore our assessment of the "Other" risk of bias item changed from "unclear" based on core reports to "high" based on full clinical study reports.
- In the treatment trials WV15819, WV15876, and WV15978, it was difficult to reconcile the total number of hospitalizations despite access to the full clinical study reports. One patient in the placebo arm who was hospitalized according to serious adverse event narratives does not appear in the hospitalizations table and for a separate placebo patient that is listed in the serious adverse event narratives, no hospitalization is described in this narrative but the same patient was hospitalized according to the hospitalizations table. It was therefore unclear how many hospitalizations occurred in the trial, to whom and why.

Risk of bias, core reports	Risk of bias, full clinical study reports			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	26 (20%)	0 (0%)	0 (0%)	**26 (20%)**
Unclear	28 (22%)	0 (0%)	14 (11%)	**42 (32%)**
Low	34 (26%)	0 (0%)	28 (22%)	**62 (48%)**
Total	**88 (68%)**	**0 (0%)**	**42 (32%)**	**130 (100%)**

Table 1. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports.

Risk of bias, core reports	Risk of bias, full clinical study reports			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	11 (8%)	15 (12%)	0 (0%)	**26 (20%)**
Unclear	1 (1%)	27 (21%)	14 (11%)	**42 (32%)**
Low	12 (9%)	22 (17%)	28 (22%)	**62 (48%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 2. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports allowing unclear assessments in sensitivity analysis.

Risk of bias, full clinical study reports	Risk of bias, full clinical study reports allowing unclear assessments			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	24 (18%)	64 (49%)	0 (0%)	**88 (68%)**
Unclear	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
Low	0 (0%)	0 (0%)	42 (32%)	**42 (32%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 3. Change in overall (all elements) risk of bias judgments for 15 full clinical study reports reports of oseltamivir trials with and without allowing unclear assessments in sensitivity analysis.

Appendix 1. Table of content of an oseltamivir clinical study report, trial WV15799.

Tamiflu® (oseltamivir phosphate)
75mg Capsules, Hard
12 mg/mL Oral Suspension

Roche

5.3.5.4.6 CSR WV15799 (W-144170)

CLINICAL STUDY REPORT MODULES

This report consists of 5 modules.

Those not supplied in this submission are obtainable from the sponsor on request.

MODULE I:	**CORE REPORT**
	Background and Rationale Objectives Materials and Methods Efficacy Results Safety Results Discussion Conclusion Appendices
MODULE II:	**STUDY DOCUMENTS**
	Protocol and Amendment History Blank Case Report Form (CRF) Subject Information Sheet and Consent Form Glossaries of Original and Preferred Terms Randomization List Reporting Analysis Plan (RAP) Certificates of Analysis List of Investigators List of Ethics Committee
MODULE III:	**LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA**
MODULE IV:	**LISTINGS OF SAFETY DATA**
MODULE V:	**STATISTICAL REPORT AND APPENDICES**
	Statistical Analysis Efficacy Results

Appendix 2. Mapping and extraction tool for oseltamivir clinical study report (CSR) Module 2 elements to Cochrane Characteristics of Included Studies elements

Mapping Tamiflu CSR Module 2 elements to Cochrane Characteristics of Included Studies elements

Aim: To identify sections of the Clinical Study Reports (CSRs) Module 2 (defined as what Roche calls "Module 2") which may improve understanding of the content of the Cochrane included studies table (CIST).

Drug:	Oseltamivir (Tamiflu)
CSR for trial(s):	
Reviewer:	
Date(s) of extraction:	

Notes:

1. **Do not remove this notice**
2. **Do not merge cells in the tables (Merged cells wreak havoc in collating answers in a spreadsheet)**
3. **Do not copy-paste images from the CSR**

Trial Summary

Trial summary given in…	Trial summary
CSR	(*Short (2-3) sentence description of the trial as given in the CSR – most likely in the Synopsis section.*)
A159 (January 2012)	(*Copy and/or assemble this from the Characteristics of Included Studies table in the A159 review published in January 2012.*)
Your own words, after extracting M2	(*Write a new trial summary that is accurate based on your understanding of the trial after reading M2.*)

Risk of bias

Bias	A159 (Jan 2012) judgment	A159 (Jan 2012) support for judgment	Reviewer's judgment (post M2)	Support for judgment
Random sequence generation (selection bias)				
Allocation				

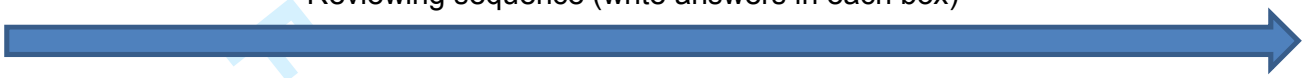
concealment (selection bias)				
Incomplete outcome data (attrition bias), symptoms				
Incomplete outcome data (attrition bias), complications of influenza				
Incomplete outcome data (attrition bias), safety data				
Selective reporting (reporting bias), other bias				
Other bias				
Blinding of participants and personnel (performance bias), all outcomes				
Blinding of outcome assessment (detection bias), all outcomes				

Trial timeline

Serial	Timeline element	Date	Version (if a version name/number is given)	Page (PDF page no.) where item can be found
A	Patient enrollment dates			
B	Unblinding of the trial			
C	Protocol for which we have the full text (if we have multiple versions in full text, record all dates and versions)			
D	Protocol amendments (list all amendments with dates and their version stamp)			
E	Statistical Analysis Plan for which we have the full text (if we have multiple versions in full text, record all dates and versions)			

F	SAP amendments (list all amendments with dates and their version stamp)			
G	Patient consent form			
H	Randomization list			
I	Certificate of Analysis			

Reviewing sequence (write answers in each box)



Serial	Cochrane Characteristics of Included Studies	Check these M2 elements with care:	Is M1 reporting consistent with M2? Yes – No – Unclear (choose one)	If the answer is no then record the difference
1	METHODS			
1a	○ Study Design	RPS		
1b	○ Location, number of centers	RPS LIESA		
1c	○ Duration of study	RPS		
2	PARTICIPANTS			
2a	○ Number screened	-	LEAVE BLANK UNLESS NEEDED	LEAVE BLANK UNLESS NEEDED
2b	○ Number randomized	-		
2c	○ Number completed	-		
2d	○ Number analysed	-		
2e	○ Male/Female ratio	-		
2f	○ Mean age	-		
2g	○ Baseline details	-		
2h	○ Inclusion criteria	RPS		
2i	○ Exclusion criteria	RPS		
2j	○ Definition of patient populations for analysis	RPS RAP		
3	INTERVENTIONS			

3a	○ Intervention	RPS CA RAP		
3b	○ Control	RPS CA RAP		
3c	○ Treatment period	RPS RAP FUC		
3d	○ Treatment duration	RPS RAP FUC		
3e	○ Follow up (in days)	RPS RAP FUC		
3f	○ Co-interventions	RPS RAP		
4	OUTCOMES			
4a	○ Primary outcome	RPS RAP CRF Note: ensure CRF can capture relevant info		
4b	○ Secondary outcomes	RPS RAP CRF Note: ensure CRF can capture relevant info		
5	NOTES			Make any other points you wish here
6	RISK OF BIAS			
6a	○ Random sequence generation (selection bias)	RPS RL		
6b	○ Allocation concealment (selection bias)	RPS		
6c	○ Incomplete outcome data (attrition bias)	RPS IC Note: IC may contain		

		details that suggest possible influence on retention or attrition		
6d	○ Selective reporting (reporting bias)	RPS IC LIESA Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	○ Other bias	RPS		
6f	○ Blinding of participants and personnel (performanc e bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR	Are the intervention and control identical in all but the active principle?	
6g	○ Blinding of outcome assessment (detection bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR		

CA = Certificate of Analysis
CRF = Case Report Form(s)
FUC = Follow up cards/Diary cards
IC = Informed Consent and participant contract
LIESA = Lists of Investigators, IRB, EC and Site Addresses
RAP = Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan (SAP))
RL = Randomisation List
RPS = Relevant Protocol Section (including latest amendments)

NOTE: Roche protocol amendments are designated with a suffix letter e.g. B, C, D. The latest version of the protocol is the one that should be followed in the trial which then assumes the suffix to denote the version followed e.g. WV 15799H.

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Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports

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Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports

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Abstract

Words: 280

Background

The Cochrane risk of bias tool is a prominent instrument used to evaluate potential biases in clinical trials. In three updates of our Cochrane review on neuraminidase inhibitors, we assessed risk of bias on the same trials using different levels of detail: the trials in journal publications, in core reports, and in full clinical study reports. Here we analyze whether progressively greater amounts of information and detail in full clinical study reports (including trial protocols, statistical analysis plans, certificates of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments.

Methods and Findings

We used the Cochrane risk of bias tool to assess and compare risk of bias in 14 oseltamivir trials (reported in 10 clinical study reports) obtained from the European Medicines Agency (EMA) and the manufacturer, Roche. With more detailed information, no previous assessment of “high” risk of bias was reclassified as “low” or “unclear” in the main analysis, and over half (55%, 34/62) of previous assessments of “low” risk of bias were reclassified as “high”. Most “unclear” risk of bias (67%, or 28/42) was reclassified as “high” risk of bias when our judgments were based on full clinical study reports. Limits of our study were our relative inexperience in dealing with large information sets, sometimes subjective bias judgments, and focus on industry trials. Comparison with journal publications was not possible because of the low number of trials published.

Conclusions

We found that as information increased in the document, this increased our assessment of bias. This may mean risk of bias has been insufficiently reported in other Cochrane review assessments limited to published research

Strengths and limitations of this study

- The availability of full clinical study reports decreased the uncertainty of bias judgments and allowed clearer judgments to be made
- The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text
- Our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents may limit our ability to assess risk of bias in clinical study reports
- The current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information. This may have impacted our findings
- The custom data extraction sheet we have developed is for use with clinical study reports, and may not apply to non-industry trials where clinical study reports usually do not exist

Introduction

The risk of bias tool in Cochrane reviews of randomized trials is routinely used to assess essential items pertaining to validity of trial design such as random sequence generation, allocation concealment, attrition and performance biases. There are six standard bias elements, each rated as either at "high", "low", or "unclear" risk of bias.

As Cochrane reviews are typically based on synthesizing studies based on reports published in the scientific literature, the risk of bias tool is traditionally applied to journal publications. To our knowledge, the ways in which risk of bias judgments change when they are based on more detailed reports of trials, such as those contained in clinical study reports, has not been previously investigated.

Clinical study reports are considered the most exhaustive summaries of randomized controlled trials of pharmaceuticals. Clinical study reports are highly structured and detailed documents that follow an outline format agreed between regulators and manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency policies adopted by the European Medicines Agency,[3] as well as announcements by some pharmaceutical companies to make clinical study reports more readily available [4,5] suggest that clinical study reports may increasingly be incorporated into systematic reviews and other forms of evidence synthesis.

Although there is some variation in the structure and content of clinical study reports, they are usually composed of a core report of the trial and appendices. A core report (sections 1-15 of the ICH E3 document) is structured in Introduction, Methods Results And Discussion (IMRAD) style. The numerous appendices (section 16 of ICH E3) contain important supplementary data needed to understand and interpret the trial, its context and history.[1,2] These appendices include such documents as the trial protocol, protocol amendments, statistical analysis plan, blank case report forms, certificates of analysis, randomization lists, and consent forms. For the purposes of this paper the core report plus all its appendices will be known as the full clinical study report. (See Appendix 1 for the table of contents of a typical oseltamivir clinical study report and http://dx.doi.org/10.5061/dryad.77471 for free download of all the clinical study reports used in our review and featured in this paper. The core report was known as Module 1 in oseltamivir clinical study reports, and appendices were found in Modules 2-5.) Core reports and full clinical study reports theoretically can help reduce uncertainty in judging risk of bias.

In 2012, we published an update of our Cochrane review of neuraminidase inhibitors which included a total of 32 oseltamivir trials.[6] Unlike most Cochrane reviews, this review was based only on core reports, [6] and risk of bias assessments were therefore based on each core report. Subsequently in 2013, we obtained full clinical study reports from Roche, and as part of a further systematic review update, carried out new risk of bias assessments of the same trials based on the full clinical study reports.

Our overall aim was to investigate whether the level of detail contained in reports of trials affects judgments about risk of bias. We planned to achieve this by comparing documents

which contain increasingly detailed information on each trial included in our review, namely journal publications, core reports, and full clinical study reports. As well as using the standard Cochrane risk of bias tool, we developed an additional list of study elements we wanted to extract in order to allow improved assessments of each trial's design and conduct and facilitate the organization of large quantities of information now available to us.

In this report we describe our use of these tools to address three specific questions:

1. Do core reports change the risk of bias evaluation compared to published papers?
2. Do full clinical study reports change the risk of bias evaluation compared to core reports?
3. Do full clinical study reports change the risk of bias evaluation compared to published papers?

Methods

Ten core reports (M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978) were received in PDF files from Roche and EMA by 12 April 2011 (the date of time-lock for our 2012 Cochrane review).[6] The reporting of more than one trial in the same clinical study report was justified by Roche as a consequence of lower than expected participant recruitment due to low influenza circulation and consequently a need to pool studies.

The current Cochrane risk of bias tool consists of six domains, each may have more than one source of bias application, depending on the subject matter.[7] Our applications were as follows: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel – all outcomes), detection bias (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms, complications and harms outcome data), reporting bias (selective reporting) and other bias. The identification of sources of other bias was left at the reviewers' discretion.

Risk of bias assessments were performed following Cochrane methods [7] and published in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis of data extracted from core reports.

After 12th April 2011, we obtained the appendices of the clinical study reports included in our review. For most clinical study reports we requested, EMA had the protocol, protocol amendments, statistical analysis plan, blank case report forms, and other appendices contained in what Roche terms the second "module" of a full clinical study report (see Appendix 1). However EMA did not possess—and therefore could not provide us with—full clinical study reports with the exception of trial WP16263.[8] For approximately three years Roche had repeatedly refused our requests for full clinical study reports.[9]

In April 2013 in the course of carrying out these new extractions, Roche changed its policy on access to data and pledged to share with us 77 full clinical study reports (www.bmj.com/tamiflu/roche). Fifteen clinical study reports containing 20 trials were included in the analysis of our current review.[10] As we were already in possession of core reports and appendices such as the protocol and statistical analysis plan for the 14

trials in this analysis, the additional data for other clinical study reports provided by Roche does not concern this paper. In the clinical study reports Roche redacted information that they judged to be of “legitimate commercial interest” or present a risk of trial participant re-identification. The redactions did not impede our analyses of risk of bias.

Based on our growing familiarity with clinical study reports, we designed and piloted a data extraction sheet to record how our understanding of the trials changed in light of availability of the additional appendices. We realized that in addition to the standard Cochrane risk of bias elements, we needed to organize the abundant material at our disposal and re-construct a timeline of the trials. We used the Cochrane risk of bias tool [7] to appraise clinical study reports and a data extraction sheet for recording information relevant to this appraisal. We added the following elements to our extraction sheets: date of participant enrollment, unblinding of the trial, protocol for which we had the full text, protocol amendments, statistical analysis plan for which we have the full text (and its amendments), patient consent form, randomization list, and certificate of analysis. Timeline reconstruction allowed us to conceptualise the design and conduct of the trials and appreciate their role in the trial programme with their strengths and limitations. In addition following a timeline allows a judgment to be made on the integrity and temporal sequence of the documents. The finalized extraction sheet is in Appendix 2.

Based on access to full clinical study reports, we carried out our final assessment of risk of bias. These were carried out by a single reviewer, checked by a second with final consensus reached through a face-to-face discussion among the entire group.

Because with full clinical study reports there should be no ambiguity, we only allowed "low" or "high" risk of bias judgments (i.e. no “unclear”). We adopted the position that, unlike a publication which may have page limits, there was no reason a full clinical study report should be missing details necessary for a third party to judge risk of bias. Therefore, when information that would have otherwise allowed us to judge a risk of bias as either "low" or "high" was missing, this would automatically be categorized as “high” risk of bias. This decision to eliminate the “unclear” option when assessing full clinical study reports was made following an initial assessment of the trials, which included “unclear” judgments. Based on earlier peer-review of this paper which suggested we analyze the data had we kept the “unclear” category, we also carried out this post-hoc analysis.

To allow for a comparison of risk of bias judgments based on published reports of trials and risk of bias judgments based on clinical study reports (either core reports alone or full clinical study reports), we used our previous risk of bias judgments for the same trials in the relevant Cochrane reviews that had been based on publications.[11,12]

The extraction and adjudication methods used were the same as those used in our subsequent unified Cochrane review.[6] We used descriptive methods to answer our three questions without the need for formal statistical analysis.

Ethics approval and patient consent were not necessary for this study.

Results

We could only compare risk of bias assessments between core reports and full clinical study reports for the following 14 trials (reported in 10 clinical study reports): M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978 (Figure 1 and Table 1).

We could not carry out a comparison of risk of bias judgments of journal publications with core reports or full clinical study reports, because our assessments were largely based on secondary publications (notably, the Kaiser et al pooled analysis of ten trials, eight of which were unpublished[13]) rather than primary publications of the trials, and also utilized an outdated risk of bias tool. There were therefore too few studies for which we had distinct risk of bias judgments of primary journal publications (many studies for which we have clinical study reports were and remain unpublished, for example 8 of the 13 trials in adults). In addition, the current Cochrane risk of bias tool was introduced after the production of our review of published articles, making the comparison, had we had the data to undertake it, more difficult to interpret and possibly unfair.

For the comparison of core and full clinical study reports, Table 2 shows that no previous assessment of "high" risk of bias was reclassified as "low" or "unclear" in the presence of more detailed information. Previous assessments of "low" risk of bias were not uncommonly reclassified as "high" bias in the subsequent assessment. While our assessments based on core reports were mostly classified as "low risk of bias" they were reclassified in the opposite direction as "high" risk of bias when our judgments were based on full clinical study reports (Table 2).

Had we kept the "unclear" risk of bias judgment option when assessing full clinical study reports [10] we would have had 64 "unclear" judgments (see sensitivity analysis in Table 3). The breakdown of these 64 into the various attributes is:

- Attrition bias: symptoms (10); complications (9); safety (15). These were unclear because we do not know the impact of missing symptoms data, the reports contained unclear definitions for secondary complications of influenza, and a seemingly problematic decision tool for the alternative designation of events as either complications or harms, which we called "compliharms" in our Cochrane review.
- Other bias (13) – these are unclear due to the unknown effect of the dehydrocholic acid included in the placebo but not included in the active treatment
- Performance bias (6) – these are unclear due to missing certificates of analysis describing the placebo appearance
- Selection bias (10) – these are unclear due to the missing or unclear randomisation lists meaning we cannot confirm random sequence generation
- Detection bias (1) – unclear due to unknown impact of different coloured placebo caps on outcome assessment

See Tables 3 and 4. Twenty nine percent of previously certain judgments (i.e. "high" or "low" risk of bias) based on core reports became "unclear" with full clinical study reports.

An example of the kind of detail available in full clinical study reports and the importance of the trial timeline in assessing presence of bias, is the observation that of the clinical study reports for the 14 trials, only 1 contained a protocol which predated the beginning of participant enrolment, only 2 had statistical analysis plans which clearly predated participants enrolment and 3 had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding. Completed extraction sheets with risk of bias comparisons and rationales are available on request from the corresponding author.

Discussion

We used the Cochrane six-item risk of bias instrument to assess bias from two different levels of detail of trial reports. Because of unrestricted access to full clinical study reports, we took the view that all information needed to judge risk of bias for each of the six domains of the Cochrane risk of bias should be present. When the information was not available, we judged the corresponding risk of bias element as being “high”. Therefore the availability of full clinical study reports decreased the uncertainty and allowed clearer judgments to be made. Risk of bias previously assessed as “unclear” based on core reports became a more certain "low" or "high" risk of bias.. When the information was not available, our judgments changed because we found gaps in the availability of information and inconsistent information. Whether the full study reports represent an exhaustive and coherent source of trial narrative and data remains unclear.

Throughout our study we were assessing two different types of material within the clinical study reports: those that were created or written prior to patient enrollment (e.g. trial protocols), and those written after (e.g. core reports).

This approach is not possible when assessing trials reported in journal publications, in which articles necessarily reflect post hoc reporting with a far more sparse level of detail. We suggest that when bias is so limiting as to make meta-analysis results unreliable, it either should not be done or a prominent explanation of its clear limitations should be included alongside the meta-analysis. We found the Cochrane risk of bias tool to be difficult to apply to clinical study reports. We think this is not because the tool was constructed to assess journal publications but as with all list-like instruments its use lends itself to a check-list approach (in which each design item is sought and, if found, eliminated from the bias equation rather than with thought and consideration). Similarly, the extraction sheet we assembled needs to be applied with thought and consideration – an approach that does not lend itself to reviewing under time pressure. However more focus should be devoted to bias itself and its effects rather than theoretical *risk* of bias. Many of the variables we found to be important when assessing the trial (e.g. date of trial protocol, date of unblinding, date of participant enrollment) are simply not captured in the risk of bias tool when used in a routine way or to review publications. We were also often unsure how to judge the risk of bias when bias itself can actually or potentially be measured with reviewers’ access to full clinical study reports and individual participant data. If, for example, the original trial protocol is available, one can judge whether reporting bias occurred. Reviewers need not guess at bias (i.e. make a judgment of “risk”) but can judge bias directly. However even with individual participant data, some forms of bias, such as

attrition bias, may still be difficult to quantify, and one can only judge the risk (i.e. potential) of bias. Therefore access to detailed information and participant level data sometimes found in full clinical study reports, provides an opportunity to consider both *actual* as well as *risk of* biases.

Box 1 shows examples of the types of information found in clinical study reports that led to risk of bias assessment changes. While the judgments of "low" or "high" risk of bias may imply certainty, particularly when based on the reading of a full clinical study report, we found ourselves often in lengthy debate and discussion over the proper level of risk of bias before arriving at a consensus. We found the risk of bias judgments themselves to carry a high level of subjectivity, in which different judgments can be justified in different ways. The real strength of the risk of bias tool appears not to be in the final judgments it enables, but rather in the process it helps facilitate: critical assessment of a clinical trial.

Another aspect to emerge is that tools based on publications are designed to detect presence, absence or uncertainty regarding elements in a very restricted number of places in the text. The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text. An example of this active engagement is the cross-checking of active principle and placebo batches used across trials and their connection with a visual description of their properties such as color in a certificate of analysis. For example, once the presence of a differently colored placebo capsule cap in trial WP16263 was identified through the clinical study report's certificate of analysis, its potential impact on blinding was captured in the Cochrane instrument. The interpretation of such a finding is difficult, as the colors of the active principle and placebo capsule caps are close (ivory and light yellow). However publication-based or core report only based assessments would not have identified the potential differences in color as the descriptions are simply given as "placebo" [14] and "matching placebo" [15] respectively. Reviewing complete clinical study reports and our assessment of bias was very time consuming, necessitating prolonged exchanges including a face-to face meeting given the novelty of what we were doing. This activity though was not as difficult or as time consuming as the reconstruction of trial evidence programmes for oseltamivir, an activity which necessitated a whole time equivalent researcher for 6 months. However because of the threat of reporting bias we can think of no alternative to the use of full clinical study reports.

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents such as randomization lists. Randomization lists appeared to be of two types. The first was a pre-randomization list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post-hoc randomization list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not provided or original codes cannot be matched to patients. Another limitation of our study is the instrument we have developed is for using with clinical study reports, and may not apply to non-industry trials (which may not have a clinical study report).

As evidence of reporting bias in industry trial publication mounts, [8,16–21] we believe Cochrane reviews should increasingly rely on clinical study reports as the basic unit of analysis. The systematic evaluation of bias or risk of bias remains an essential aspect of evidence synthesis, as it forces reviewers to critically examine trials. However, the current Cochrane risk of bias tool does not sufficiently identify possible faults with study design nor does it help to organize and check coherence of large amounts of information that are found in clinical study reports. Our experience suggests that more detailed extraction sheets that prompt reviewers to consider additional aspects of study may be needed. Until a more appropriate guide is developed, we offer our custom extraction sheets to Cochrane reviewers and others interested in assessing risk of bias using clinical study reports and encourage further development.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

An ethics statement was not required for this work.

Contributorship statement. All authors fulfil all three of the ICMJE guidelines for authorship which are 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Competing interests

Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as 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 FDA). Dr Jefferson was a consultant for IMS Health in 2013 and is currently retained as a scientific advisor to a legal team acting on the drug Tamiflu (oseltamivir, Roche). Dr Jefferson recently had part of his expenses reimbursed for attending the annual (UK) Pharmaceutical Statisticians' Conference.

Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Dr Doshi is an associate editor at The BMJ.

Dr Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and receives fees for editorial and guideline developmental work and royalties from books and

in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled “Tamiflu: harmful as was afraid” and “In order to escape from drug-induced encephalopathy”. Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.

Data Sharing. The source core reports and clinical study reports can be found at <http://datadryad.org/resource/doi:10.5061/dryad.77471>. A spreadsheet recording all individual risk of bias judgments is available in an online supplemental file to this paper.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 [cited 2012 Jul 8]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

2. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open. 2013 Feb 26;3(2):e002496.

3. European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043 [Internet]. 2010 [cited 2012 May 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf

4. F. Hoffmann-La Roche Ltd. Roche Global Policy on Sharing of Clinical Trials Data [Internet]. 2013 [cited 2013 Jun 19]. Available from: http://roche-trials.com/dataSharingPolicy.action

5. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. N Engl J Med. 2013;369(5):475–8.

6. Jefferson T, Jones MA, Doshi P, et al.Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;(1):CD008965.

7. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

8. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. BMJ. 2012 Jan 17;344:d7898.

9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med. 2012 Apr 10;9(4):e1001201.

10. Jefferson T, Jones M, Doshi P, et al.Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

11. Wang K, Shun-Shin M, Gill P, et al. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744.

12. Jefferson T, Jones M, Doshi P, et al.. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2010;2:CD001265.

13. Kaiser L, Wat C, Mills T, Mahoney P, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul 28;163(14):1667–72.

14. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 May;35(5):461–7.

15. Hoffman-La Roche, Ltd. Clinical Study Report – Protocol WP16263. A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Report No. 1003328. 2001.

16. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.

17. Vedula SS, Bero L, Scherer RW, et al. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963–71.

18. Vedula SS, Li T, Dickersin K. Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-Label Uses of Gabapentin. PLoS Med. 2013 Jan 29;10(1):e1001378.

19. Rodgers MA, Brown JVE, Heirs MK, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ. 2013;346:f3981.

20. Eyding D, Lelgemann M, Grouven U, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341(oct12 1):c4737–c4737.

21. Wieseler B, Wolfram N, McGauran N, et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med. 2013 Oct 8;10(10):e1001526.

22. Jefferson TO, Demicheli V, Di Pietrantonj C, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2009;2:CD001265.

23. Matheson NJ, Harnden AR, Perera R, et al. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev Online. 2007;(1):CD002744.

Box 1: Examples of risk of bias assessment changes and other concerns

- In trial WV15708, the risk of bias related to allocation concealment went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because the full clinical study report did not report sufficient details about the method of allocation concealment.
- In trial WV15707, the risk of bias related to random sequence generation went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because a full description of the randomization procedure was not provided.
- Prophylaxis trials WV15673 and WV15697 are described as "identical" but this could not be verified as we only had one protocol (and the protocol we did have was dated after study completion). In addition, the placebo event rates for influenza infection were very different between the two trials and their pooling, combined with the redaction of center numbers, preventing from being individually added to a meta-analysis. Therefore our assessment of the "Other" risk of bias item changed from "unclear" based on core reports to "high" based on full clinical study reports.
- In the treatment trials WV15819, WV15876, and WV15978, it was difficult to reconcile the total number of hospitalizations despite access to the full clinical study reports. One patient in the placebo arm who was hospitalized according to serious adverse event narratives does not appear in the hospitalizations table and for a separate placebo patient that is listed in the serious adverse event narratives, no hospitalization is described in this narrative but the same patient was hospitalized according to the hospitalizations table. It was therefore unclear how many hospitalizations occurred in the trial, to whom and why.
- In prophylaxis trials WV15673 and WV15697, bias was assessed as low for selective reporting because the intention-to-treat population was described and reported in a table. However when the full clinical study report became available we realised that the original protocol was missing.

	Risk of bias assessment performed based on			
Trial(s)	**Pooled analysis** [13] (2009 Cochrane review[22])	**Journal publication** (2007, 2009 and 2010 Cochrane reviews [12,22,23])	**Core report** (2012 Cochrane review [6])	**Full clinical study report** (2014 Cochrane review [10])
M76001	x		x	x
NV16871			x	x
WV15670		x	x	x
WV15671		x	x	x
WV15707	x		x	x
WV15730	x		x	x
WV15759 WV15871			x	x
WV15799		x	x	x
WV15812 WV15872	x		x	x
WV15819 WV15876 WV15978	x		x	x

Table 1. Risk of bias assessments performed by trial, 2009-2014.

Risk of bias, core reports	**Risk of bias, full clinical study reports**			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	26 (20%)	0 (0%)	0 (0%)	**26 (20%)**
Unclear	28 (22%)	0 (0%)	14 (11%)	**42 (32%)**
Low	34 (26%)	0 (0%)	28 (22%)	**62 (48%)**
Total	**88 (68%)**	**0 (0%)**	**42 (32%)**	**130 (100%)**

Table 2. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports.

Risk of bias, core reports	**Risk of bias, full clinical study reports**			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	11 (8%)	15 (12%)	0 (0%)	**26 (20%)**
Unclear	1 (1%)	27 (21%)	14 (11%)	**42 (32%)**
Low	12 (9%)	22 (17%)	28 (22%)	**62 (48%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 3. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports including unclear assessments.

Risk of bias, full clinical study reports	Risk of bias, full clinical study reports allowing unclear assessments			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	24 (18%)	64 (49%)	0 (0%)	**88 (68%)**
Unclear	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
Low	0 (0%)	0 (0%)	42 (32%)	**42 (32%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 4. Change in overall (all elements) risk of bias judgments for 15 full clinical study reports reports of oseltamivir trials with and without allowing unclear assessments.

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Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full ~~journal publications and unpublished~~ clinical study reports

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Abstract

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Background

The Cochrane risk of bias tool is a prominent instrument used to evaluate potential biases in clinical trials. In three updates of our Cochrane review on neuraminidase inhibitors, we assessed risk of bias on the same trials using different levels of detail: the trials in journal publications, in core reports, and in full clinical study reports. Here we analyze whether progressively greater amounts of information and detail in full clinical study reports (including trial protocols, statistical analysis plans, certificates of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments.

Methods and Findings

We used ~~and extended~~ the Cochrane risk of bias tool to assess and compare risk of bias in 14 oseltamivir trials (reported in 10 clinical study reports) obtained from the European Medicines Agency (EMA) and ~~its~~ the manufacturer, Roche. With more detailed information, no previous assessment of "high" risk of bias was reclassified as "low" or "unclear" in the main analysis, and over half (55%, 34/62) of previous assessments of "low" risk of bias were reclassified as "high". Most "unclear" risk of bias (67%, or 28/42) was reclassified as "high" risk of bias when our judgments were based on full clinical study reports. Limits of our study were our relative inexperience in dealing with large information sets, sometimes subjective bias judgments, and focus on industry trials. Comparison with journal publications was not possible because of the low number of trials published~~publication bias the limits of the Cochrane tool~~.

Conclusions

We found that as information increased in the document, this increased our assessment of bias. This may mean risk of bias has been insufficiently reported in other Cochrane review assessments limited to published research

~~The current Cochrane risk of bias tool is primarily designed to aid the critical evaluation of trials published in journal publications, but full clinical study reports~~ and participant level ~~data in some cases may allow for bias to be actually measured rather than reported as an un-quantified risk. Further development~~ and application to other trial programmes by other ~~investigators is now needed~~may be necessary.~~

Strengths and limitations of this study

- The availability of full clinical study reports decreased the uncertainty of biase judgementss and allowed definitiveclearer judgments to be made
- The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text.
- Our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents may limit our ability to assess risk of bias in clinical study reports findings
- The current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information that are found in clinical study reports. This may have impacted our findings.
- The custom data extraction sheetinstrument we have developed is for use with clinical study reports, and may not apply to non-industry trials becausewhere clinical study reports usually do not exist

Introduction

The risk of bias tool in Cochrane reviews of randomized trials is routinely used to assess essential items pertaining to validity of trial design ~~standard items considered critical to trial study design~~ such as random sequence generation, allocation concealment, attrition and performance biases. There are six standard bias elements, each rated as either at "high", "low", or "unclear" risk of bias.

As Cochrane reviews are ~~mostly~~typically based on synthesizing studies based on reports published in the scientific literature, the risk of bias tool is traditionally applied to journal publications. To our knowledge, ~~how~~ the ways in which risk of bias judgments ~~may~~ change when they are based on more detailed reports of trials, such as those contained in clinical study reports, has not been previously investigated.

Clinical study reports are considered the most exhaustive summaries of randomized controlled trials of pharmaceuticals. Clinical study reports are highly structured and detailed documents that follow an outline format agreed between regulators and manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency policies adopted by the European Medicines Agency,[3] as well as ~~recent~~ announcements by some pharmaceutical companies to make clinical study reports more readily available [4,5] suggest that clinical study reports may increasingly be incorporated into systematic reviews and other forms of evidence synthesis.

Although there is some variation in the structure and content of clinical study reports, they are usually composed of a core~~main~~ report of the trial ~~(sections 1-15 of the ICH E3 document, called a "core report" in oseltamivir clinical study reports)~~ and appendices ~~(section 16 of ICH E3)~~. A core report (sections 1-15 of the ICH E3 document) is structured in Introduction, Methods Results A~~a~~nd Discussion (IMRAD) style. ~~that is accompanied by~~ The numerous appendices~~, which~~ (section 16 of ICH E3) contain important supplementary data needed to understand and interpret the trial, its context and history ~~(section 16 of ICH E3)~~.[1,2] These appendices include such documents as the trial protocol, protocol amendments, statistical analysis plan, blank case report forms, certificates of analysis, randomization lists, and ~~informed~~ consent forms. For the purposes of this paper the core report plus all its appendices ~~(roughly equivalent to modules II to V in oseltamivir clinical study reports)~~ will be known as the full clinical study report. (S~~ee~~ Appendi~~x~~ 1 for ~~an index~~the table of contents of a typical oseltamivir clinical study report and http://dx.doi.org/10.5061/dryad.77471 for free download of all the clinical study reports used in our review and featured in~~s~~ this paper~~)~~. The core report was known as Module 1 in oseltamivir clinical study reports, and appendices were found in M~~m~~odules 2-5.)

~~Such documents~~Core reports and full clinical study reports theoretically can help reduce uncertainty in judging risk of bias.

In 2012, we published an update of our Cochrane review of neuraminidase inhibitors ~~for~~ which included a total of 32 oseltamivir trials ~~were eligible~~.[6] Unlike most Cochrane reviews, this review was based only on core reports, ~~-~~[6] and r~~R~~isk of bias assessments were therefore ~~therefore~~ based on each ~~clinical study report's c~~core report. Subsequently

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in 2013, we obtained full clinical study reports from Roche, and as part of a further systematic review update, carried out new risk of bias assessments of the same trials based on the full clinical study reports.

We Our overall aim was aimed to investigate whether and how the level of detail contained in reports ofing a trials affectss judgments about risk of bias. We planned to achieve this, by comparing documents which containing increasingly detailed reportsinformation on each trial included in our review, namely journal publications, core reports, and full clinical study reports. for each trial included in our reviews by comparing reports of the same trial with widely varying level of detail. These were journal publications, core reports, and full clinical study reports. As well as using the standard Cochrane risk of bias tool, we developed an additional list of study elements we wanted to extract in order to allow improved assessments of to help us better judge eeach trial's design and conduct and help us in the task offacilitate the organization of organizing large quantities of information now available to us.

In this report we describe our use of these tools to address three specific questions:

1. Do core reports change the risk of bias evaluation compared to published papers?
2. Do full clinical study reports change the risk of bias evaluation compared to core reports?
3. Do full clinical study reports change the risk of bias evaluation compared to published papers?

In summary we intended to analyze whether progressively greater amounts of information and detail in clinical study reports (including trial protocols, statistical analysis plans, certificate of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments

Methods

Ten Ccore reports for 14 trials contained in 10 Clinical study reports (M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978; NV16871) were received in pdfPDF files from Roche and EMA by 12 April 2011 (the date of time-lock for our 2012 Cochrane review).[6] The reporting of more than one trial in the same clinical study report was justified by Roche as a consequence of lower than expected participant recruitment due to low influenza circulation and consequently a need to pool studies.

The current Cochrane risk of bias tool was first introduced in 2010. The tool consists of six domains, each may have more than one source of bias application, depending on the subject matter.[7] Our applications were as follows: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel – all outcomes), detection bias (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms, complications and harms outcome data), reporting bias (selective reporting) and other bias. The identification of sources of other bias was left at the reviewers' discretion.

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~~The reporting of more than one trial in the same clinical study report is unusual.~~was ~~justified by Roche gave~~with ~~low influenza circulation and the consequent need to pool studies as the reason.~~

R~~Trial r~~isk of bias assessments were performed following Cochrane methods [7] and published in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis of data extracted from core reports. ~~Risk of bias assessments were re-extracted from the 2012 review for this study.~~

After 12th ~~In~~ April 2011, we obtained ~~began to obtain~~ the appendices of the clinical study reports included in our review. For most clinical study reports we requested, EMA had the protocol, protocol amendments, statistical analysis plan, blank case report forms, and other appendices contained in what Roche terms the second "module" of a full clinical study report (see Appendix 1). However EMA did not possess—and therefore could not provide us with—full clinical study reports with the exception of trial WP16263.[8] For approximately three years Roche had repeatedly refused our requests for full clinical study reports.[9]

In April 2013 ~~i~~In the course of carrying out these new extractions, Roche changed its policy on access to data and pledged ~~in April 2013~~ to share with us 77 full clinical study reports (www.bmj.com/tamiflu/roche). Fifteen clinical study reports containing ~~T~~twenty20 trials were included in the analysis of our current review~~s~~.[10] As we were already in possession of core reports and appendices such as the protocol and statistical analysis plan for the 14 trials in this analysis, the additional data for other clinical study reports provided by Roche does not concern this paper. In the c~~C~~linical study reports Roche redacted information that they judged to be of "legitimate commercial interest" or present a risk of trial participant re-identification. T~~For our purposes, t~~he redactions did not impede ~~an~~ our analysei~~s~~ of risk of bias.

Based on our growing familiarity with clinical study reports, we designed and piloted a ~~custom n~~ data extraction sheet to record how our understanding of the trials changed in light of availability of the additional appendices. We realized that in addition to the standard Cochrane risk of bias elements, we needed to organize the abundant material at our disposal and re-construct a timeline of the trials. We used the Cochrane risk of bias tool ~~[9]~~[7] to appraise clinical study reports and a ~~custom built~~ data extraction sheet for recording information relevant to this appraisal. ~~We~~ We added the following elements to our ~~custom built Cochrane risk of bias tool based~~ extraction sheets: date of participant enrollment, unblinding of the trial, protocol for which we had the full text, protocol amendments, statistical analysis plan for which we have the full text (and its amendments), patient consent form, randomization list, and certificate of analysis. Timeline reconstruction allowed us to conceptualise the design and ~~running~~conduct of the trials and appreciate their role in the trial programme with their strengths and limitations. In addition following a timeline allows a judgment to be made on the integrity and temporal sequence of the documents. The finalized ~~custom~~ extraction sheet is in Appendix 2.

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Based on access to full clinical study reports, we carried out our final assessment of risk of bias. These were carried out by a single reviewer, checked by a second with final consensus reached through a face-to-face discussion among the entire group.

Because with full clinical study reports there should be no ambiguity, we only allowed "low" or "high" risk of bias judgments (i.e. no “unclear”). We adopted the position that, unlike a publication which may have page limits, there was no reason a full clinical study report should be missing details necessary for a third party to judge risk of bias. Therefore, when information that would have otherwise allowed us to judge a risk of bias as either "low" or "high" was missing, this would automatically be categorized as “high” risk of bias. This decision to eliminate the “unclear” option when assessing full clinical study reports was made following an initial assessment of the trials, which included “unclear” judgments. One Based on earlier peer-reviewer of this paper howeverwhich suggested we analyze the data had we kept the “unclear” judgmentcategory, so we also carried out this post-hoc analysis.

To allow for a comparison of risk of bias judgments based on published reports of trials and risk of bias judgments based on clinical study reports (either core reports alone or full clinical study reports), we used our previous risk of bias judgments for the same trials in the relevant Cochrane reviews that had been based on publications.[11,12]

The extraction and adjudication methods used were the same as those used in our subsequent unified Cochrane review.[6]

We used descriptive methods to answer our three questions without the need for formal statistical analysis.

Ethics approval and patient consent forms are not provided as they are not necessary for a Cochrane review, of which this study is a productwere not necessary for this study.

Results

We could only compare risk of bias assessments between core reports and full clinical study reports where we had a record of risk of bias assessments that were based on, firstly, core reports alone, and then, full clinical study reports. We had these for the following 14 trials (reported in 10 clinical study reports): M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978; NV16871WV15730, WV15707, M76001, WV15812 WV15872, WV15819/WV15876/WV15978, WV15670, WV15671, NV16871, WV15759/WV15871, WV15799 (Figure 1 and Table 1).

We could not carry out a comparison of risk of bias judgments of journal publications with core reports or full clinical study reports, because our assessments were largely based on secondary publications (includenotably, in the Kaiser et al pooled analysis of ten trials, eight of which were unpublished[13]) and notrather than primary publications of the trials, and also utilized an outdated risk of bias tool. There were therefore too few studies for which we had distinct risk of bias judgments of primary journal publications (many studies

for which we have clinically study reports were and remain unpublished, for example 8 of the 13 trials in adults). In addition, the current Cochrane risk of bias tool was introduced after the production of our review based onof published articles, making the comparison, had we had the data to undertake it, more difficult to interpret and possibly unfair.

For the comparison of core and complete full clinical study reports, Table 1 2 shows that no previous assessment of "high" risk of bias was reclassified as "low" or "unclear" in the presence of more detailed information. Previous assessments of "low" risk of bias were not uncommonly reclassified as "high" bias in the subsequent assessment. While our assessments based on core reports were mostly classified as "low risk of bias" they were reclassified in the opposite direction as "high" risk of bias when our judgments were based on full clinical study reports (Table 12).

A spreadsheet recording all individual risk of bias judgments is available in an online supplemental file.

Had we kept the "unclear" risk of bias judgment option when assessing full clinical study reports [10] we would have had 64 "unclear" judgments (see sensitivity analysis in Table 3). The breakdown of these 64 into the various attributes is:

- Attrition bias: symptoms (10); complications (9); safety (15). These were unclear because we do not know the impact of missing symptoms data, the reports contained unclear definitions for secondary complications of influenza, and a seemingly problematic decision tool for the alternative designation of events as either complications or harms, which we called "compliharms" in our Cochrane review.
- Other bias (13) – these are unclear due to the unknown effect of the de-hydrochlolric acid included in the placebo but not included in the active treatment
- Performance bias (6) – these are unclear due to missing certificates of analysis describing the placebo appearance
- Selection bias (10) – these are unclear due to the missing or unclear randomisation lists meaning we cannot confirm random sequence generation
- Detection bias (1) – unclear due to unknown impact of different coloured placebo caps on outcome assessment

See Tables 32 and 34. Twenty nine percent of previously certain judgments (i.e. "high" or "low" risk of bias) based on core reports became "unclear" with full clinical study reports.

An example of the kind of detail available in full clinical study reports and the importance of the trial timeline in assessing presence of bias, is the observation that of the clinical study reports for the 14 trials, only 1 contained a protocol which predated the beginning of participant enrolment, only 2 had statistical analysis plans which clearly predated participants enrolment and 3 had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding.

Completed extraction sheets with risk of bias comparisons and rationales are available on request from the corresponding author.

Discussion

We used the Cochrane six-item risk of bias instrument to assess bias ~~under~~ from two different levels of detail ~~in~~ of trial report~~sing~~. ~~The availability of full clinical study reports decreased the uncertainty and allowed definitive judgments to be made. "Unclear" risk of bias became a more certain "low" or "high" risk of bias, or even certainty of bias. Certainty or low levels of uncertainty were recorded against instances where our expectations of having all relevant and consistent information available for our reviews.~~ Because of unrestricted access to full clinical study reports, we took the view that all information needed to judge risk of bias for each of the six domains of the Cochrane risk of bias should be present. When the information was not available, we judged the corresponding risk of bias element as being "high". Therefore the availability of full clinical study reports decreased the uncertainty and allowed clearer ~~definitive~~ judgments to be made. ~~"Unclear" r~~Risk of bias previously assessed as "unclear" based on core reports became a more certain "low" or "high" risk of bias. ~~, or even certainty of bias.~~ When the information was not available, our judgments changed because we found gaps in the availability of information and inconsistent information. Whether the full study reports represent an exhaustive and coherent source of trial narrative and data remains unclear.

Throughout our study we were assessing two different types of material within the clinical study reports: those that were created or written prior to patient enrollment (e.g. trial protocols), and those written after (e.g. core reports).

This approach is not possible when assessing trials reported in journal publications, in which articles necessarily reflect post hoc reporting ~~at~~ with a far more sparse level of detail. We suggest that when bias is so limiting as to make meta-analysis results unreliable, it either should not be done or a prominent explanation of its clear limitations should be ~~posted~~ included alongside the meta-analysis. We found the Cochrane risk of bias tool to be difficult to apply to clinical study reports. We think this is not because the tool was constructed to assess journal publications but as with all list-like instruments its use lends itself to a check-list approach (in which each design item is sought and, if found, eliminated from the bias equation rather than with thought and consideration). Similarly, the ~~instrument~~ extraction sheet we assembled needs to be applied with thought and consideration – an approach that does not lend itself to reviewing under time pressure. However more focus should be devoted to bias itself and its effects rather than theoretical *risk* of bias. Many of the variables we found to be important when assessing the trial (e.g. date of trial protocol, date of unblinding, date of participant enrollment) are simply not captured in the risk of bias tool when used in a routine way or to review publications. We were also often unsure how to judge the risk of bias when bias itself can actually or potentially be measured with reviewers' access to ~~individual participant data given the detailed data available which is sometimes available in~~ full clinical study reports and individual participant data. If, for example, the ~~detailed information about participants that withdrew from the trial~~original trial protocol is available, one can judge whether ~~this attrition~~reporting bias occurred ~~created an actual bias or not. With patient level data, which can be available in CSRs but hard to analyse in "paper" form, r~~Reviewers ~~have the option to~~need not ~~simply~~ guess at bias (i.e. make a judgment of "risk") but can ~~measure~~judge bias

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using the complete datasetdirectly. However even with individual participant data, some forms of bias, such as attrition bias, may still be difficult to if In such a situation it is impossible to quantify bias because withdrawals are lost, it seems to make little sense toquantify, and one can only judge the risk (i.e. potential) of attrition bias, but this is what the Cochrane tool asks us to do. Therefore access to detailed information and participant level data sometimes found in full clinical study reports, affordprovides an the opportunity to think aboutconsider both *actual* as well asand *risk of* biases.

Box 1 shows examples of the types of information found in clinical study reports that led to risk of bias assessment changes. While the judgments of "low" or "high" risk of bias may portrayimply certainty, particularly when based on the reading of a full clinical study report, we found ourselves often in lengthy debate and discussion over the proper level of risk of bias before arriving at a consensus. We found the risk of bias judgments themselves to carry a great high levelamount of subjectivity, in which different judgments can be justified in different ways. The real strength of the risk of bias tool appears not to be in the final judgments it enables, but rather in the process it helps facilitate: critical assessment of a clinical trial.

Another aspect that to emerges became obvious is that tools based on publications are designed to detect presence, absence or uncertainty regarding elements in a very restricted number of places in the text. The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text. An example of this active engagement is the cross-checking of active principle and placebo batches used across trials and their connection with a visual description of their properties such as color in a certificate of analysis. For example, once the presence of a differently colored placebo capsule cap in trial WP16263 was identified through the clinical study report's certificate of analysis, its potential impact on blinding was captured in the Cochrane instrument. The interpretation of such a finding is open to questiondifficult, as the colors of the active principle and placebo capsule caps are close (ivory and light yellow). However publication-based or core report only based assessments would not have identified the potential differences in color as the descriptions are simply given are as "placebo" [14] and "matching placebo" [15] respectively. Reviewing complete clinical study reports and our assessment of bias was very time consuming, necessitating prolonged exchanges including a face-to face meeting given the absolute novelty of what we were doing. This activity though was not as difficult or as time consuming as the reconstruction of trial evidence programmes for oseltamivir, an activity which necessitated a whole time equivalent researcher for 6 months. However because of the threat of reporting bias we can think of no alternative to the use of full clinical study reports.

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents such as randomization lists. Randomization lists appeared to be of two types. The first was a pre-randomization list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post-hoc randomization list to which individual participants can be matched but the original

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generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not provided or original codes cannot be matched to patients. Another limitation of our study is the instrument we have developed is for using with clinical study reports, and may not apply to non-industry trials (which may not have a clinical study report).

As evidence of reporting bias in industry trial publication mounts, [8,16–21] we believe Cochrane reviews should increasingly rely on clinical study reports as the basic unit of analysis. The systematic evaluation of bias or risk of bias remains an essential aspect of evidence synthesis, as it forces reviewers to critically examine trials. However, the current Cochrane risk of bias tool ~~is not adequate for the task as it~~ does not sufficiently ~~reliably~~ identify possible faults with study design ~~all types of important biases~~ nor does it help to organize and check coherence of large amounts of information that are found in clinical study reports. Our experience suggests that more detailed extraction sheets that prompt reviewers to consider additional aspects of study may be needed. Until a more appropriate guide ~~instrument~~ is developed, we offer~~propose~~ our custom extraction sheets ~~tool~~ to Cochrane reviewers and others interested in assessing risk of bias using clinical study reports and encourage further development. ~~as a possible interim measure to be used and adapted across a wide range of clinical study reports.~~

Data sharing: A spreadsheet recording all individual risk of bias judgments will be posted on dryad: www.datadryad.org.

Acknowledgements. We thank Toby Lasserson for providing advice and an independent check of our risk of bias judgments.

Funding. This project was funded by the NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series. Visit the HTA programme web site for more details: http://www.nets.nihr.ac.uk/projects/hta/108001. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. The National Institute of Health Research (NIHR) School of Primary Care Research (SPCR) provides financial support for Dr Carl Heneghan.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

An ethics statement was not required for this work.

Contributorship statement. All authors fulfil~~s~~ all three of the ICMJE guidelines for authorship which are '1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the

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version to be published.~~' If anyone currently listed as an author doesn't fulfil all three of these then they should be moved to the acknowledgment section.~~

~~**Financial Disclosures**~~ **Competing interests**

Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as 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 FDA). Dr Jefferson was a consultant for IMS Health in 2013 and is currently retained as a scientific advisor to a legal team acting on the drug Tamiflu (oseltamivir, Roche). Dr Jefferson recently had part of his expenses reimbursed for attending the annual (UK) Pharmaceutical Statisticians' Conference.

Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Dr Doshi is an associate editor at The BMJ.

Dr Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and receives fees for editorial and guideline developmental work and royalties from books and in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled "Tamiflu: harmful as was afraid" and "In order to escape from drug-induced encephalopathy". Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

~~Drs Jefferson, Jones, Heneghan, Doshi, Del Mar, Thompson and Hama are co-recipients 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 - http: //www.hta.ac.uk/2352).~~

Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.

Data Sharing. The source core reports and clinical study reports can be found at <http://datadryad.org/resource/doi:10.5061/dryad.77471>. A spreadsheet recording all individual risk of bias judgments is available in an online supplemental file to this paper.

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References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 [cited 2012 Jul 8]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

2. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open. 2013 Feb 26;3(2):e002496.

3. European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043 [Internet]. 2010 [cited 2012 May 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf

4. F. Hoffmann-La Roche Ltd. Roche Global Policy on Sharing of Clinical Trials Data [Internet]. 2013 [cited 2013 Jun 19]. Available from: http://roche-trials.com/dataSharingPolicy.action

5. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. N Engl J Med. 2013;369(5):475–8.

6. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;(1):CD008965.

7. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

8. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. BMJ. 2012 Jan 17;344:d7898.

9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med. 2012 Apr 10;9(4):e1001201.

10. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

11. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744.

12. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2010;2:CD001265.

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13. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul 28;163(14):1667–72.

14. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 May;35(5):461–7.

15. Hoffman-La Roche, Ltd. Clinical Study Report – Protocol WP16263. A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Report No. 1003328. 2001.

16. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.

17. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963–71.

18. Vedula SS, Li T, Dickersin K. Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-Label Uses of Gabapentin. PLoS Med. 2013 Jan 29;10(1):e1001378.

19. Rodgers MA, Brown JVE, Heirs MK, Higgins JPT, Mannion RJ, Simmonds MC, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ. 2013;346:f3981.

20. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341(oct12 1):c4737–c4737.

21. Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med. 2013 Oct 8;10(10):e1001526.

22. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2009;2:CD001265.

23. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev Online. 2007;(1):CD002744.

Box 1: Examples of risk of bias assessment changes and other concerns

- In trial WV15708, the risk of bias related to allocation concealment went from "Unclear" based on core reports to "High" risk of bias based on full clinical study reports because the full clinical study report did not report sufficient details about the method of allocation concealment.
- In trial WV15707, the risk of bias related to random sequence generation went from "Unclear" based on core reports to "High" risk of bias based on full clinical study reports because a full description of the randomization procedure was not provided.
- Prophylaxis trials WV15673 and WV15697 are described as "identical" but this could not be verified as we only had one protocol (and the protocol we did have was dated after study completion). In addition, the placebo event rates for influenza infection were very different between the two trials and their pooling, combined with the redaction of center numbers, preventing from being individually added to a meta-analysis. Therefore our assessment of the "Other" risk of bias item changed from "unclear" based on core reports to "high" based on full clinical study reports.
- In the treatment trials WV15819, WV15876, and WV15978, it was difficult to reconcile the total number of hospitalizations despite access to the full clinical study reports. One patient in the placebo arm who was hospitalized according to serious adverse event narratives does not appear in the hospitalizations table and for a separate placebo patient that is listed in the serious adverse event narratives, no hospitalization is described in this narrative but the same patient was hospitalized according to the hospitalizations table. It was therefore unclear how many hospitalizations occurred in the trial, to whom and why.
- In prophylaxis trials WV-15673 and WV/15697, bias was assessed as low for selective reporting because the ITTintention-to-treat population was described and reported in a table. However when the full CSRclinical study report became available we realised that the original protocol was missing.

~~Trial(s)~~	Risk of bias~~OB~~ assessment performed based on			
Trial(s)	Pooled analysis [13] (2009 Cochrane review[22]~~)~~)	Journal publication (2007, 2009 and 2010 Cochrane reviews [12,22,23])	Core report (2012 Cochrane review [6]~~–~~)	Full clinical study report (2014 Cochrane review [10])
M76001	x		x	x
NV16871			x	x
WV15670		x	x	x
WV15671		x	x	x
WV15707	x		x	x
WV15730	x		x	x
WV15759 WV15871			x	x
WV15799		x	x	x
WV15812 WV15872	x		x	x
WV15819 WV15876 WV15978	x		x	x

Table 1. Risk of bias~~OB~~ assessments performed~~,~~ by trial, 2009-2014.

Risk of bias, core reports	Risk of bias, full clinical study reports			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	26 (20%)	0 (0%)	0 (0%)	**26 (20%)**
Unclear	28 (22%)	0 (0%)	14 (11%)	**42 (32%)**
Low	34 (26%)	0 (0%)	28 (22%)	**62 (48%)**
Total	**88 (68%)**	**0 (0%)**	**42 (32%)**	**130 (100%)**

Table 2~~1~~. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports.

Risk of bias, core reports	Risk of bias, full clinical study reports			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	11 (8%)	15 (12%)	0 (0%)	**26 (20%)**
Unclear	1 (1%)	27 (21%)	14 (11%)	**42 (32%)**
Low	12 (9%)	22 (17%)	28 (22%)	**62 (48%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 3~~2~~. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports ~~allowing~~ including unclear assessments ~~in sensitivity analysis~~.

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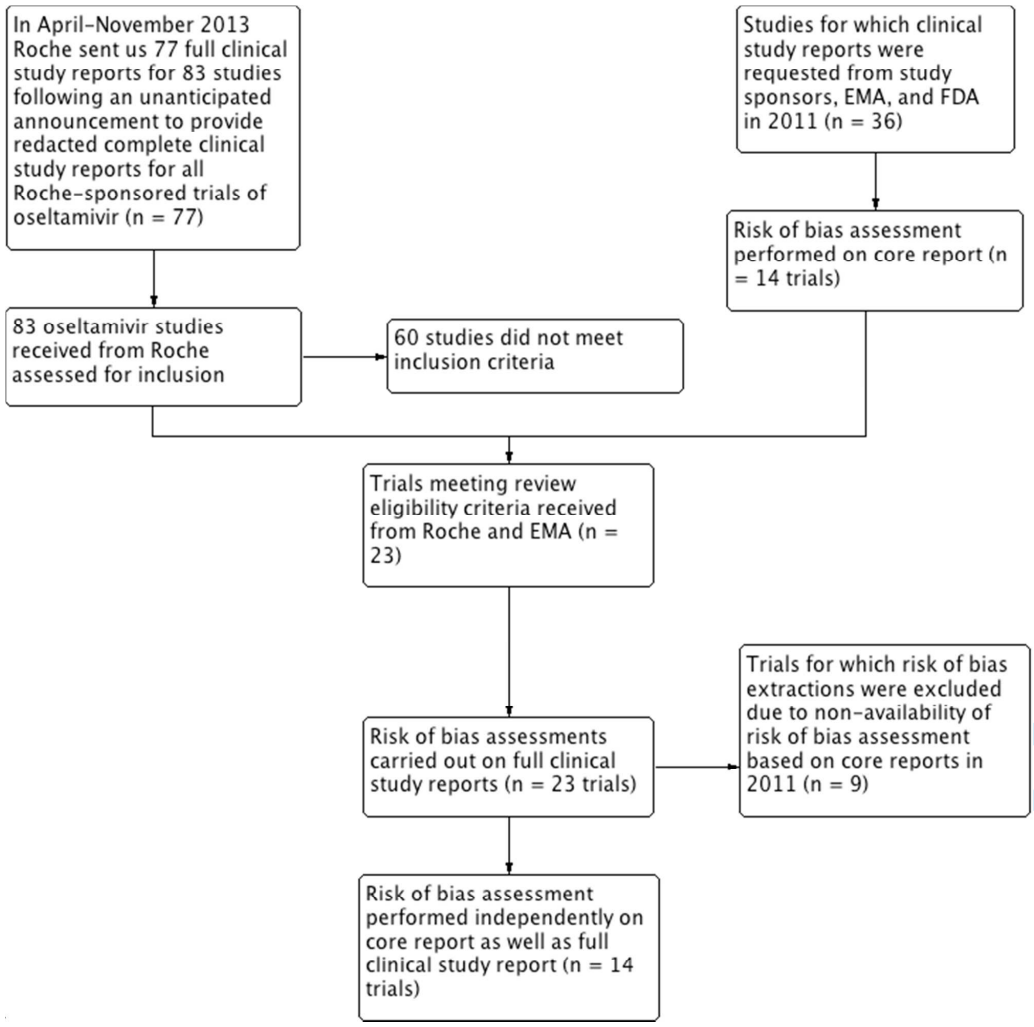
Risk of bias, full clinical study reports	Risk of bias, full clinical study reports allowing unclear assessments			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	24 (18%)	64 (49%)	0 (0%)	**88 (68%)**
Unclear	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
Low	0 (0%)	0 (0%)	42 (32%)	**42 (32%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 43. Change in overall (all elements) risk of bias judgments for 15 full clinical study reports reports of oseltamivir trials with and without allowing unclear assessments ~~in sensitivity analysis~~.



~~Figure 1. Study flow diagram~~

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Appendix 1. Table of content of an oseltamivir clinical study report, trial WV15799.

Tamiflu® (oseltamivir phosphate)
75mg Capsules, Hard
12 mg/mL Oral Suspension

Roche

5.3.5.4.6 CSR WV15799 (W-144170)

CLINICAL STUDY REPORT MODULES

This report consists of 5 modules.

Those not supplied in this submission are obtainable from the sponsor on request.

MODULE I: CORE REPORT

Background and Rationale
Objectives
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Efficacy Results
Safety Results
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Protocol and Amendment History
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Efficacy Results

Appendix 2. Mapping and extraction tool for oseltamivir clinical study report (CSR) Module 2 elements to Cochrane Characteristics of Included Studies elements

Mapping Tamiflu CSR Module 2 elements to Cochrane Characteristics of Included Studies elements

Aim: To identify sections of the Clinical Study Reports (CSRs) Module 2 (defined as what Roche calls "Module 2") which may improve understanding of the content of the Cochrane included studies table (CIST).

Drug:	Oseltamivir (Tamiflu)
CSR for trial(s):	
Reviewer:	
Date(s) of extraction:	

Notes:

1. **Do not remove this notice**
2. **Do not merge cells in the tables (Merged cells wreak havoc in collating answers in a spreadsheet)**
3. **Do not copy-paste images from the CSR**

Trial Summary

Trial summary given in…	Trial summary
CSR	(*Short (2-3) sentence description of the trial as given in the CSR – most likely in the Synopsis section.*)
A159 (January 2012)	(*Copy and/or assemble this from the Characteristics of Included Studies table in the A159 review published in January 2012.*)
Your own words, after extracting M2	(*Write a new trial summary that is accurate based on your understanding of the trial after reading M2.*)

Risk of bias

Bias	A159 (Jan 2012) judgment	A159 (Jan 2012) support for judgment	Reviewer's judgment (post M2)	Support for judgment
Random sequence generation (selection bias)				
Allocation				

concealment (selection bias)				
Incomplete outcome data (attrition bias), symptoms				
Incomplete outcome data (attrition bias), complications of influenza				
Incomplete outcome data (attrition bias), safety data				
Selective reporting (reporting bias), other bias				
Other bias				
Blinding of participants and personnel (performance bias), all outcomes				
Blinding of outcome assessment (detection bias), all outcomes				

Trial timeline

Serial	Timeline element	Date	Version (if a version name/number is given)	Page (PDF page no.) where item can be found
A	Patient enrollment dates			
B	Unblinding of the trial			
C	Protocol for which we have the full text (if we have multiple versions in full text, record all dates and versions)			
D	Protocol amendments (list all amendments with dates and their version stamp)			
E	Statistical Analysis Plan for which we have the full text (if we have multiple versions in full text, record all dates and versions)			

F	SAP amendments (list all amendments with dates and their version stamp)			
G	Patient consent form			
H	Randomization list			
I	Certificate of Analysis			

Reviewing sequence (write answers in each box)

Serial	Cochrane Characteristics of Included Studies	Check these M2 elements with care:	Is M1 reporting consistent with M2? Yes – No – Unclear (choose one)	If the answer is no then record the difference
1	METHODS			
1a	○ Study Design	RPS		
1b	○ Location, number of centers	RPS LIESA		
1c	○ Duration of study	RPS		
2	PARTICIPANTS			
2a	○ Number screened	-	LEAVE BLANK UNLESS NEEDED	LEAVE BLANK UNLESS NEEDED
2b	○ Number randomized	-		
2c	○ Number completed	-		
2d	○ Number analysed	-		
2e	○ Male/Female ratio	-		
2f	○ Mean age	-		
2g	○ Baseline details	-		
2h	○ Inclusion criteria	RPS		
2i	○ Exclusion criteria	RPS		
2j	○ Definition of patient populations for analysis	RPS RAP		
3	INTERVENTIONS			

3a	○ Intervention	RPS CA RAP		
3b	○ Control	RPS CA RAP		
3c	○ Treatment period	RPS RAP FUC		
3d	○ Treatment duration	RPS RAP FUC		
3e	○ Follow up (in days)	RPS RAP FUC		
3f	○ Co-interventions	RPS RAP		
4	OUTCOMES			
4a	○ Primary outcome	RPS RAP CRF Note: ensure CRF can capture relevant info		
4b	○ Secondary outcomes	RPS RAP CRF Note: ensure CRF can capture relevant info		
5	NOTES			Make any other points you wish here
6	RISK OF BIAS			
6a	○ Random sequence generation (selection bias)	RPS RL		
6b	○ Allocation concealment (selection bias)	RPS		
6c	○ Incomplete outcome data (attrition bias)	RPS IC Note: IC may contain		

		details that suggest possible influence on retention or attrition		
6d	○ Selective reporting (reporting bias)	RPS IC LIESA Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	○ Other bias	RPS		
6f	○ Blinding of participants and personnel (performanc e bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR	Are the intervention and control identical in all but the active principle?	
6g	○ Blinding of outcome assessment (detection bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR		

CA = Certificate of Analysis
CRF = Case Report Form(s)
FUC = Follow up cards/Diary cards
IC = Informed Consent and participant contract
LIESA = Lists of Investigators, IRB, EC and Site Addresses
RAP = Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan (SAP))
RL = Randomisation List
RPS = Relevant Protocol Section (including latest amendments)

NOTE: Roche protocol amendments are designated with a suffix letter e.g. B, C, D. The latest version of the protocol is the one that should be followed in the trial which then assumes the suffix to denote the version followed e.g. WV 15799H.

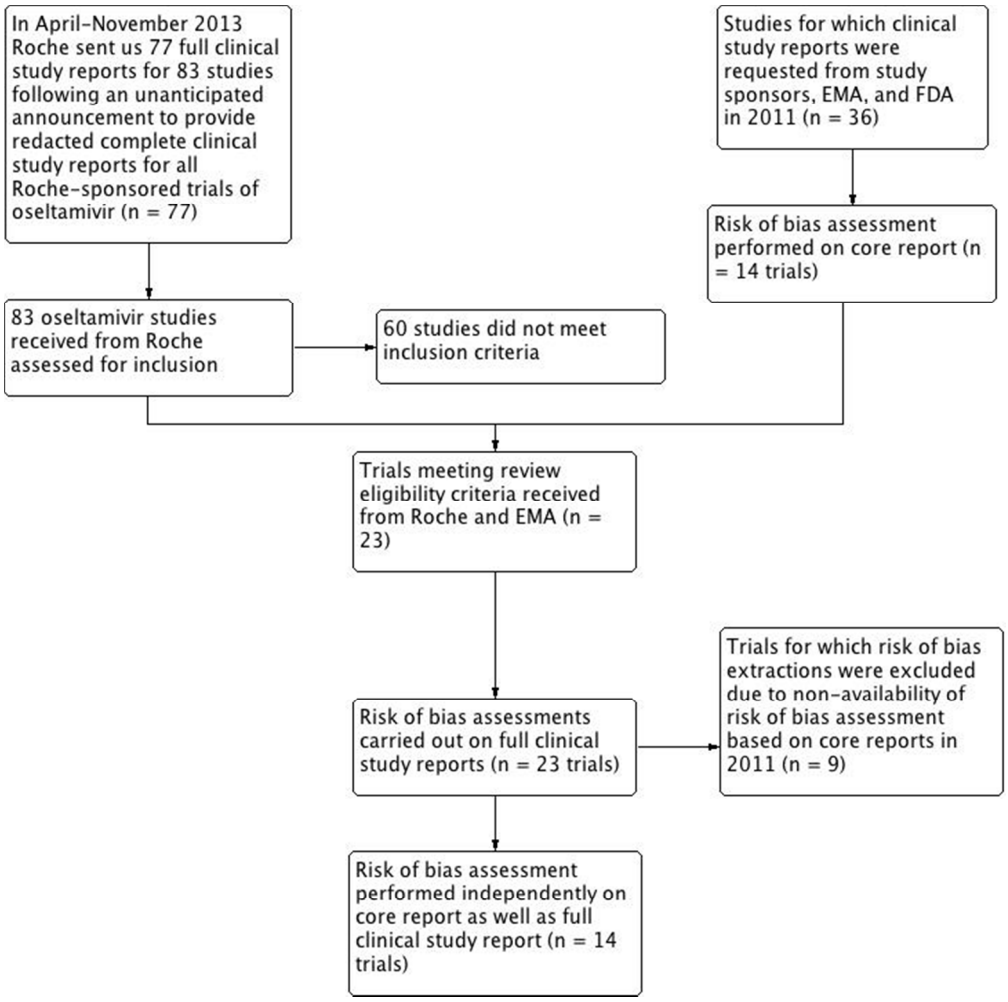

Figure 1 Flow Chart
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1	METHODS			
1a	○ Study Design	RPS		
1b	○ Location, number of centers	RPS LIESA		
1c	○ Duration of study	RPS		
2	PARTICIPANTS			
2a	○ Number screened	-	LEAVE BLANK UNLESS NEEDED	LEAVE BLANK UNLESS NEEDED
2b	○ Number randomized	-		
2c	○ Number completed	-		
2d	○ Number analysed	-		
2e	○ Male/Female ratio	-		
2f	○ Mean age	-		
2g	○ Baseline details	-		
2h	○ Inclusion criteria	RPS		
2i	○ Exclusion criteria	RPS		
2j	○ Definition of patient populations for analysis	RPS RAP		
3	INTERVENTIONS			

3a	○ Intervention	RPS CA RAP		
3b	○ Control	RPS CA RAP		
3c	○ Treatment period	RPS RAP FUC		
3d	○ Treatment duration	RPS RAP FUC		
3e	○ Follow up (in days)	RPS RAP FUC		
3f	○ Co-interventions	RPS RAP		
4	OUTCOMES			
4a	○ Primary outcome	RPS RAP CRF Note: ensure CRF can capture relevant info		
4b	○ Secondary outcomes	RPS RAP CRF Note: ensure CRF can capture relevant info		
5	NOTES			Make any other points you wish here
6	RISK OF BIAS			
6a	○ Random sequence generation (selection bias)	RPS RL		
6b	○ Allocation concealment (selection bias)	RPS		
6c	○ Incomplete outcome data (attrition bias)	RPS IC Note: IC may contain		

		details that suggest possible influence on retention or attrition		
6d	○ Selective reporting (reporting bias)	RPS IC LIESA Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	○ Other bias	RPS		
6f	○ Blinding of participants and personnel (performanc e bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR	Are the intervention and control identical in all but the active principle?	
6g	○ Blinding of outcome assessment (detection bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR		

CA = Certificate of Analysis
CRF = Case Report Form(s)
FUC = Follow up cards/Diary cards
IC = Informed Consent and participant contract
LIESA = Lists of Investigators, IRB, EC and Site Addresses
RAP = Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan (SAP))
RL = Randomisation List
RPS = Relevant Protocol Section (including latest amendments)

NOTE: Roche protocol amendments are designated with a suffix letter e.g. B, C, D. The latest version of the protocol is the one that should be followed in the trial which then assumes the suffix to denote the version followed e.g. WV 15799H.

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Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports

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Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports

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Abstract

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Background

The Cochrane risk of bias tool is a prominent instrument used to evaluate potential biases in clinical trials. In three updates of our Cochrane review on neuraminidase inhibitors, we assessed risk of bias on the same trials using different levels of detail: the trials in journal publications, in core reports, and in full clinical study reports. Here we analyze whether progressively greater amounts of information and detail in full clinical study reports (including trial protocols, statistical analysis plans, certificates of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments.

Methods and Findings

We used the Cochrane risk of bias tool to assess and compare risk of bias in 14 oseltamivir trials (reported in 10 clinical study reports) obtained from the European Medicines Agency (EMA) and the manufacturer, Roche. With more detailed information, reported in clinical study reports, no previous assessment of “high” risk of bias was reclassified as “low” or “unclear” in the main analysis, and over half (55%, 34/62) of previous assessments of “low” risk of bias were reclassified as “high”. Most “unclear” risk of bias (67%, or 28/42) was reclassified as “high” risk of bias when our judgments were based on full clinical study reports. Limits of our study were our relative inexperience in dealing with large information sets, sometimes subjective bias judgments, and focus on industry trials. Comparison with journal publications was not possible because of the low number of trials published.

Conclusions

We found that as information increased in the document, this increased our assessment of bias. This may mean risk of bias has been insufficiently assessed in Cochrane reviews based on journal publications.

Strengths and limitations of this study

- The availability of full clinical study reports decreased the uncertainty of bias judgments and allowed clearer judgments to be made
- The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text
- Our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents may limit our ability to assess risk of bias in clinical study reports
- The current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information. This may have impacted our findings
- The custom data extraction sheet we have developed is for use with clinical study reports, and may not apply to non-industry trials where clinical study reports usually do not exist

Introduction

The risk of bias tool in Cochrane reviews of randomized trials is routinely used to assess essential items pertaining to validity of trial design such as random sequence generation, allocation concealment, attrition and performance biases. There are six standard bias elements, each rated as either at "high", "low", or "unclear" risk of bias.

As Cochrane reviews are typically based on synthesizing studies based on reports published in the scientific literature, the risk of bias tool is traditionally applied to journal publications. To our knowledge, the ways in which risk of bias judgments change when they are based on more detailed reports of trials, such as those contained in clinical study reports, has not been previously investigated.

Clinical study reports are considered the most exhaustive summaries of randomized controlled trials of pharmaceuticals. Clinical study reports are highly structured and detailed documents that follow an outline format agreed between regulators and manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency policies adopted by the European Medicines Agency,[3] as well as announcements by some pharmaceutical companies to make clinical study reports more readily available [4,5] suggest that clinical study reports may increasingly be incorporated into systematic reviews and other forms of evidence synthesis.

Although there is some variation in the structure and content of clinical study reports, they are usually composed of a core report of the trial and appendices. A core report (sections 1-15 of the ICH E3 document) is structured in Introduction, Methods Results And Discussion (IMRAD) style. The numerous appendices (section 16 of ICH E3) contain important supplementary data needed to understand and interpret the trial, its context and history.[1,2] These appendices include such documents as the trial protocol, protocol amendments, statistical analysis plan, blank case report forms, certificates of analysis, randomization lists, and consent forms. For the purposes of this paper the core report plus all its appendices will be known as the full clinical study report. (See Appendix 1 for the table of contents of a typical oseltamivir clinical study report and http://dx.doi.org/10.5061/dryad.77471 for free download of all the clinical study reports used in our review and featured in this paper. The core report was known as Module 1 in oseltamivir clinical study reports, and appendices were found in Modules 2-5.) Core reports and full clinical study reports theoretically can help reduce uncertainty in judging risk of bias.

In 2012, we published an update of our Cochrane review of neuraminidase inhibitors which included a total of 32 oseltamivir trials.[6] Unlike most Cochrane reviews, this review was based only on core reports, [6] and risk of bias assessments were therefore based on each core report. Subsequently in 2013, we obtained full clinical study reports from Roche, and as part of a further systematic review update, carried out new risk of bias assessments of the same trials based on the full clinical study reports.

Our overall aim was to investigate whether the level of detail contained in reports of trials affects judgments about risk of bias. We planned to achieve this by comparing documents

which contain increasingly detailed information on each trial included in our review, namely journal publications, core reports, and full clinical study reports. As well as using the standard Cochrane risk of bias tool, we developed an additional list of study elements we wanted to extract in order to allow improved assessments of each trial's design and conduct and facilitate the organization of large quantities of information now available to us.

In this report we describe our use of these tools to address three specific questions:

1. Do core reports change the risk of bias evaluation compared to published papers?
2. Do full clinical study reports change the risk of bias evaluation compared to core reports?
3. Do full clinical study reports change the risk of bias evaluation compared to published papers?

Methods

Ten core reports (M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978) were received in PDF files from Roche and EMA by 12 April 2011 (the date of time-lock for our 2012 Cochrane review).[6] The reporting of more than one trial in the same clinical study report was justified by Roche as a consequence of lower than expected participant recruitment due to low influenza circulation and consequently a need to pool studies.

The current Cochrane risk of bias tool consists of six domains, each may have more than one source of bias application, depending on the subject matter.[7] Our applications were as follows: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel – all outcomes), detection bias (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms, complications and harms outcome data), reporting bias (selective reporting) and other bias. The identification of sources of other bias was left at the reviewers' discretion.

Risk of bias assessments were performed following Cochrane methods [7] and published in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis of data extracted from core reports.

After 12th April 2011, we obtained the appendices of the clinical study reports included in our review. For most clinical study reports we requested, EMA had the protocol, protocol amendments, statistical analysis plan, blank case report forms, and other appendices contained in what Roche terms the second "module" of a full clinical study report (see Appendix 1). However EMA did not possess—and therefore could not provide us with—full clinical study reports with the exception of trial WP16263.[8] For approximately three years Roche had repeatedly refused our requests for full clinical study reports.[9]

In April 2013 in the course of carrying out these new extractions, Roche changed its policy on access to data and pledged to share with us 77 full clinical study reports (www.bmj.com/tamiflu/roche). Fifteen clinical study reports containing 20 trials were included in the analysis of our current review.[10] As we were already in possession of core reports and appendices such as the protocol and statistical analysis plan for the 14

trials in this analysis, the additional data for other clinical study reports provided by Roche does not concern this paper. In the clinical study reports Roche redacted information that they judged to be of “legitimate commercial interest” or present a risk of trial participant re-identification. The redactions did not impede our analyses of risk of bias.

Based on our growing familiarity with clinical study reports, we designed and piloted a data extraction sheet to record how our understanding of the trials changed in light of availability of the additional appendices. We realized that in addition to the standard Cochrane risk of bias elements, we needed to organize the abundant material at our disposal and re-construct a timeline of the trials. We used the Cochrane risk of bias tool [7] to appraise clinical study reports and a data extraction sheet for recording information relevant to this appraisal. We added the following elements to our extraction sheets: date of participant enrollment, unblinding of the trial, protocol for which we had the full text, protocol amendments, statistical analysis plan for which we have the full text (and its amendments), patient consent form, randomization list, and certificate of analysis. Timeline reconstruction allowed us to conceptualise the design and conduct of the trials and appreciate their role in the trial programme with their strengths and limitations. In addition following a timeline allows a judgment to be made on the integrity and temporal sequence of the documents. The finalized extraction sheet is in Appendix 2.

Based on access to full clinical study reports, we carried out our final assessment of risk of bias. These were carried out by a single reviewer, checked by a second with final consensus reached through a face-to-face discussion among the entire group.

Because with full clinical study reports there should be no ambiguity, we only allowed "low" or "high" risk of bias judgments (i.e. no “unclear”). We adopted the position that, unlike a publication which may have page limits, there was no reason a full clinical study report should be missing details necessary for a third party to judge risk of bias. Therefore, when information that would have otherwise allowed us to judge a risk of bias as either "low" or "high" was missing, this would automatically be categorized as “high” risk of bias. This decision to eliminate the “unclear” option when assessing full clinical study reports was made following an initial assessment of the trials, which included “unclear” judgments. Based on earlier peer-review of this paper which suggested we analyze the data had we kept the “unclear” category, we also carried out this post-hoc analysis.

To allow for a comparison of risk of bias judgments based on published reports of trials and risk of bias judgments based on clinical study reports (either core reports alone or full clinical study reports), we used our previous risk of bias judgments for the same trials in the relevant Cochrane reviews that had been based on publications.[11,12]

The extraction and adjudication methods used were the same as those used in our subsequent unified Cochrane review.[6] We used descriptive methods to answer our three questions without the need for formal statistical analysis.

Ethics approval and patient consent were not necessary for this study.

Results

We could only compare risk of bias assessments between core reports and full clinical study reports for the following 14 trials (reported in 10 clinical study reports): M76001; NV16871; WV15670; WV1Z5671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978 (Figure 1 and Table 1).

We could not carry out a comparison of risk of bias judgments of journal publications with core reports or full clinical study reports, because our assessments were largely based on secondary publications (notably, the Kaiser et al pooled analysis of ten trials, eight of which were unpublished[13]) rather than primary publications of the trials, and also utilized an outdated risk of bias tool. There were therefore too few studies (3) for which we had distinct risk of bias judgments of primary journal publications (many studies for which we have clinical study reports were and remain unpublished, for example 8 of the 13 trials in adults). In addition, the current Cochrane risk of bias tool was introduced after the production of our review of published articles, making the comparison, had we had the data to undertake it, more difficult to interpret and possibly unfair.

For the comparison of core and full clinical study reports, Table 2 shows that no previous assessment of "high" risk of bias was reclassified as "low" or "unclear" in the presence of more detailed information. Previous assessments of "low" risk of bias were not uncommonly reclassified as "high" bias in the subsequent assessment. While our assessments based on core reports were mostly classified as "low risk of bias" they were reclassified in the opposite direction as "high" risk of bias when our judgments were based on full clinical study reports (Table 2).

A spreadsheet recording all individual risk of bias judgments is available on line, see supplemental file 1.

Had we kept the "unclear" risk of bias judgment option when assessing full clinical study reports [10] we would have had 64 "unclear" judgments (see sensitivity analysis in Table 3). The breakdown of these 64 into the various attributes is:

- Attrition bias: symptoms (10); complications (9); safety (15). These were unclear because we do not know the impact of missing symptoms data, the reports contained unclear definitions for secondary complications of influenza, and a seemingly problematic decision tool for the alternative designation of events as either complications or harms, which we called "compliharms" in our Cochrane review.
- Other bias (13) – these are unclear due to the unknown effect of the dehydrocholic acid included in the placebo but not included in the active treatment
- Performance bias (6) – these are unclear due to missing certificates of analysis describing the placebo appearance
- Selection bias (10) – these are unclear due to the missing or unclear randomisation lists meaning we cannot confirm random sequence generation
- Detection bias (1) – unclear due to unknown impact of different coloured placebo caps on outcome assessment

See Tables 3 and 4. Twenty nine percent of previously certain judgments (i.e. “high” or “low” risk of bias) based on core reports became “unclear” with full clinical study reports.

An example of the kind of detail available in full clinical study reports and the importance of the trial timeline in assessing presence of bias, is the observation that of the clinical study reports for the 14 trials, only 1 contained a protocol which predated the beginning of participant enrolment, only 2 had statistical analysis plans which clearly predated participants enrolment and 3 had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding. Completed extraction sheets with risk of bias comparisons and rationales are available on request from the corresponding author.

Discussion

We used the Cochrane six-item risk of bias instrument to assess bias from two different levels of detail of trial reports. Because of unrestricted access to full clinical study reports, we took the view that all information needed to judge risk of bias for each of the six domains of the Cochrane risk of bias should be present. When the information was not available, we judged the corresponding risk of bias element as being “high”. Therefore the availability of full clinical study reports decreased the uncertainty and allowed clearer judgments to be made. Risk of bias previously assessed as “unclear” based on core reports became a more certain "low" or "high" risk of bias.. When the information was not available, our judgments changed because we found gaps in the availability of information and inconsistent information. Whether the full study reports represent an exhaustive and coherent source of trial narrative and data remains unclear.

Throughout our study we were assessing two different types of material within the clinical study reports: those that were created or written prior to patient enrollment (e.g. trial protocols), and those written after (e.g. core reports).

This approach is not possible when assessing trials reported in journal publications, in which articles necessarily reflect post hoc reporting with a far more sparse level of detail. We suggest that when bias is so limiting as to make meta-analysis results unreliable, it either should not be done or a prominent explanation of its clear limitations should be included alongside the meta-analysis. We found the Cochrane risk of bias tool to be difficult to apply to clinical study reports. We think this is not because the tool was constructed to assess journal publications but as with all list-like instruments its use lends itself to a check-list approach (in which each design item is sought and, if found, eliminated from the bias equation rather than with thought and consideration). Similarly, the extraction sheet we assembled needs to be applied with thought and consideration – an approach that does not lend itself to reviewing under time pressure. However more focus should be devoted to bias itself and its effects rather than theoretical *risk* of bias. Many of the variables we found to be important when assessing the trial (e.g. date of trial protocol, date of unblinding, date of participant enrollment) are simply not captured in the risk of bias tool when used in a routine way or to review publications. We were also often unsure how to judge the risk of bias when bias itself can actually or potentially be measured with reviewers’ access to full clinical study reports and individual participant data. If, for

example, the original trial protocol is available, one can judge whether reporting bias occurred. Reviewers need not guess at bias (i.e. make a judgment of "risk") but can judge bias directly. However even with individual participant data, some forms of bias, such as attrition bias, may still be difficult to quantify, and one can only judge the risk (i.e. potential) of bias. Therefore access to detailed information and participant level data sometimes found in full clinical study reports, provides an opportunity to consider both *actual* as well as *risk of* biases.

Box 1 shows examples of the types of information found in clinical study reports that led to risk of bias assessment changes. While the judgments of "low" or "high" risk of bias may imply certainty, particularly when based on the reading of a full clinical study report, we found ourselves often in lengthy debate and discussion over the proper level of risk of bias before arriving at a consensus. We found the risk of bias judgments themselves to carry a high level of subjectivity, in which different judgments can be justified in different ways. The real strength of the risk of bias tool appears not to be in the final judgments it enables, but rather in the process it helps facilitate: critical assessment of a clinical trial.

Another aspect to emerge is that tools based on publications are designed to detect presence, absence or uncertainty regarding elements in a very restricted number of places in the text. The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text. An example of this active engagement is the cross-checking of active principle and placebo batches used across trials and their connection with a visual description of their properties such as color in a certificate of analysis. For example, once the presence of a differently colored placebo capsule cap in trial WP16263 was identified through the clinical study report's certificate of analysis, its potential impact on blinding was captured in the Cochrane instrument. The interpretation of such a finding is difficult, as the colors of the active principle and placebo capsule caps are close (ivory and light yellow). However publication-based or core report only based assessments would not have identified the potential differences in color as the descriptions are simply given as "placebo" [14] and "matching placebo" [15] respectively. Reviewing complete clinical study reports and our assessment of bias was very time consuming, necessitating prolonged exchanges including a face-to face meeting given the novelty of what we were doing. This activity though was not as difficult or as time consuming as the reconstruction of trial evidence programmes for oseltamivir, an activity which necessitated a whole time equivalent researcher for 6 months. However because of the threat of reporting bias we can think of no alternative to the use of full clinical study reports.

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents such as randomization lists. Randomization lists appeared to be of two types. The first was a pre-randomization list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post-hoc randomization list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not

provided or original codes cannot be matched to patients. Another limitation of our study is the instrument we have developed is for using with clinical study reports, and may not apply to non-industry trials (which may not have a clinical study report).

The background to our use of clinical study reports was our mistrust of journal publications of oseltamivir trials. Many trials were unpublished, and of those published, we found and documented examples of reporting bias. At least one trial publication was drafted by an unnamed medical writer. As evidence of reporting bias in industry trial publication mounts, [8,16–21] we believe Cochrane reviews should increasingly rely on clinical study reports as the basic unit of analysis. Sponsors and researchers both have a responsibility to make all efforts to make full clinical study reports publicly available. The systematic evaluation of bias or risk of bias remains an essential aspect of evidence synthesis, as it forces reviewers to critically examine trials. However, the current Cochrane risk of bias tool does not sufficiently identify possible faults with study design nor does it help to organize and check coherence of large amounts of information that are found in clinical study reports. Our experience suggests that more detailed extraction sheets that prompt reviewers to consider additional aspects of study may be needed. Until a more appropriate guide is developed, we offer our custom extraction sheets to Cochrane reviewers and others interested in assessing risk of bias using clinical study reports and encourage further development.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

An ethics statement was not required for this work.

Contributorship statement. All authors were involved in the design of the study and the linked Cochrane review. The custom data extraction sheet was designed by TJ, MJ, CH, and PD. All authors extracted the data as described and interpreted it. MJ carried out statistical analyses. TJ wrote the first draft of the manuscript and all authors contributed to subsequent drafts.

Competing interests

Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as 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 FDA). Dr Jefferson was a consultant for IMS Health in 2013 and is currently retained as a scientific advisor to a legal team acting on the drug Tamiflu (oseltamivir, Roche). Dr Jefferson recently had part of his expenses reimbursed for attending the annual (UK) Pharmaceutical Statisticians' Conference.

Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Dr Doshi is an associate editor at The BMJ.

Dr Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and receives fees for editorial and guideline developmental work and royalties from books and in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled "Tamiflu: harmful as was afraid" and "In order to escape from drug-induced encephalopathy". Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.

Data Sharing. The source core reports and clinical study reports can be found at <http://datadryad.org/resource/doi:10.5061/dryad.77471>. A spreadsheet recording all individual risk of bias judgments is available in an online supplemental file to this paper.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 [cited 2012 Jul 8]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

2. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open. 2013 Feb 26;3(2):e002496.

3. European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043 [Internet]. 2010 [cited 2012 May 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf

4. F. Hoffmann-La Roche Ltd. Roche Global Policy on Sharing of Clinical Trials Data [Internet]. 2013 [cited 2013 Jun 19]. Available from: http://roche-trials.com/dataSharingPolicy.action

5. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. N Engl J Med. 2013;369(5):475–8.

6. Jefferson T, Jones MA, Doshi P, et al.Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;(1):CD008965.

7. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

8. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. BMJ. 2012 Jan 17;344:d7898.

9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med. 2012 Apr 10;9(4):e1001201.

10. Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

11. Wang K, Shun-Shin M, Gill P, et al. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744.

12. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2010;2:CD001265.

13. Kaiser L, Wat C, Mills T, Mahoney P, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul 28;163(14):1667–72.

14. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 May;35(5):461–7.

15. Hoffman-La Roche, Ltd. Clinical Study Report – Protocol WP16263. A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Report No. 1003328. 2001.

16. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.

17. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963–71.

18. Vedula SS, Li T, Dickersin K. Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-Label Uses of Gabapentin. PLoS Med. 2013 Jan 29;10(1):e1001378.

19. Rodgers MA, Brown JVE, Heirs MK, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ. 2013;346:f3981.

20. Eyding D, Lelgemann M, Grouven U, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341(oct12 1):c4737–c4737.

21. Wieseler B, Wolfram N, McGauran N, et al.Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med. 2013 Oct 8;10(10):e1001526.

22. Jefferson TO, Demicheli V, Di Pietrantonj C, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2009;2:CD001265.

23. Matheson NJ, Harnden AR, Perera R, et al. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev Online. 2007;(1):CD002744.

Box 1: Examples of risk of bias assessment changes and other concerns

- In trial WV15708, the risk of bias related to allocation concealment went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because the full clinical study report did not report sufficient details about the method of allocation concealment.
- In trial WV15707, the risk of bias related to random sequence generation went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because a full description of the randomization procedure was not provided.
- Prophylaxis trials WV15673 and WV15697 are described as "identical" but this could not be verified as we only had one protocol (and the protocol we did have was dated after study completion). In addition, the placebo event rates for influenza infection were very different between the two trials and their pooling, combined with the redaction of center numbers, preventing from being individually added to a meta-analysis. Therefore our assessment of the "Other" risk of bias item changed from "unclear" based on core reports to "high" based on full clinical study reports.
- In the treatment trials WV15819, WV15876, and WV15978, it was difficult to reconcile the total number of hospitalizations despite access to the full clinical study reports. One patient in the placebo arm who was hospitalized according to serious adverse event narratives does not appear in the hospitalizations table and for a separate placebo patient that is listed in the serious adverse event narratives, no hospitalization is described in this narrative but the same patient was hospitalized according to the hospitalizations table. It was therefore unclear how many hospitalizations occurred in the trial, to whom and why.
- In prophylaxis trials WV15673 and WV15697, bias was assessed as low for selective reporting because the intention-to-treat population was described and reported in a table. However when the full clinical study report became available we realised that the original protocol was missing.

Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports

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Abstract

Words: 280

Background

The Cochrane risk of bias tool is a prominent instrument used to evaluate potential biases in clinical trials. In three updates of our Cochrane review on neuraminidase inhibitors, we assessed risk of bias on the same trials using different levels of detail: the trials in journal publications, in core reports, and in full clinical study reports. Here we analyze whether progressively greater amounts of information and detail in full clinical study reports (including trial protocols, statistical analysis plans, certificates of analyses, individual participant data listings and randomization lists) affected our risk of bias assessments.

Methods and Findings

We used the Cochrane risk of bias tool to assess and compare risk of bias in 14 oseltamivir trials (reported in 10 clinical study reports) obtained from the European Medicines Agency (EMA) and the manufacturer, Roche. With more detailed information, reported in clinical study reports, no previous assessment of "high" risk of bias was reclassified as "low" or "unclear" in the main analysis, and over half (55%, 34/62) of previous assessments of "low" risk of bias were reclassified as "high". Most "unclear" risk of bias (67%, or 28/42) was reclassified as "high" risk of bias when our judgments were based on full clinical study reports. Limits of our study were our relative inexperience in dealing with large information sets, sometimes subjective bias judgments, and focus on industry trials. Comparison with journal publications was not possible because of the low number of trials published.

Conclusions

We found that as information increased in the document, this increased our assessment of bias. This may mean risk of bias has been insufficiently ~~reported~~ assessed in ~~other~~ Cochrane reviews ~~assessments limited to~~ based on ~~published research~~journal publications.

Strengths and limitations of this study

- The availability of full clinical study reports decreased the uncertainty of bias judgments and allowed clearer judgments to be made
- The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text
- Our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents may limit our ability to assess risk of bias in clinical study reports
- The current Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all types of important biases nor does it organize and check coherence of large amounts of information. This may have impacted our findings
- The custom data extraction sheet we have developed is for use with clinical study reports, and may not apply to non-industry trials where clinical study reports usually do not exist

Introduction

The risk of bias tool in Cochrane reviews of randomized trials is routinely used to assess essential items pertaining to validity of trial design such as random sequence generation, allocation concealment, attrition and performance biases. There are six standard bias elements, each rated as either at "high", "low", or "unclear" risk of bias.

As Cochrane reviews are typically based on synthesizing studies based on reports published in the scientific literature, the risk of bias tool is traditionally applied to journal publications. To our knowledge, the ways in which risk of bias judgments change when they are based on more detailed reports of trials, such as those contained in clinical study reports, has not been previously investigated.

Clinical study reports are considered the most exhaustive summaries of randomized controlled trials of pharmaceuticals. Clinical study reports are highly structured and detailed documents that follow an outline format agreed between regulators and manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency policies adopted by the European Medicines Agency,[3] as well as announcements by some pharmaceutical companies to make clinical study reports more readily available [4,5] suggest that clinical study reports may increasingly be incorporated into systematic reviews and other forms of evidence synthesis.

Although there is some variation in the structure and content of clinical study reports, they are usually composed of a core report of the trial and appendices. A core report (sections 1-15 of the ICH E3 document) is structured in Introduction, Methods Results And Discussion (IMRAD) style. The numerous appendices (section 16 of ICH E3) contain important supplementary data needed to understand and interpret the trial, its context and history.[1,2] These appendices include such documents as the trial protocol, protocol amendments, statistical analysis plan, blank case report forms, certificates of analysis, randomization lists, and consent forms. For the purposes of this paper the core report plus all its appendices will be known as the full clinical study report. (See Appendix 1 for the table of contents of a typical oseltamivir clinical study report and http://dx.doi.org/10.5061/dryad.77471 for free download of all the clinical study reports used in our review and featured in this paper. The core report was known as Module 1 in oseltamivir clinical study reports, and appendices were found in Modules 2-5.) Core reports and full clinical study reports theoretically can help reduce uncertainty in judging risk of bias.

Field Code Changed

In 2012, we published an update of our Cochrane review of neuraminidase inhibitors which included a total of 32 oseltamivir trials.[6] Unlike most Cochrane reviews, this review was based only on core reports, [6] and risk of bias assessments were therefore based on each core report. Subsequently in 2013, we obtained full clinical study reports from Roche, and as part of a further systematic review update, carried out new risk of bias assessments of the same trials based on the full clinical study reports.

Our overall aim was to investigate whether the level of detail contained in reports of trials affects judgments about risk of bias. We planned to achieve this by comparing documents

which contain increasingly detailed information on each trial included in our review, namely journal publications, core reports, and full clinical study reports. As well as using the standard Cochrane risk of bias tool, we developed an additional list of study elements we wanted to extract in order to allow improved assessments of each trial's design and conduct and facilitate the organization of large quantities of information now available to us.

In this report we describe our use of these tools to address three specific questions:

1. Do core reports change the risk of bias evaluation compared to published papers?
2. Do full clinical study reports change the risk of bias evaluation compared to core reports?
3. Do full clinical study reports change the risk of bias evaluation compared to published papers?

Methods

Ten core reports (M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978) were received in PDF files from Roche and EMA by 12 April 2011 (the date of time-lock for our 2012 Cochrane review).[6] The reporting of more than one trial in the same clinical study report was justified by Roche as a consequence of lower than expected participant recruitment due to low influenza circulation and consequently a need to pool studies.

The current Cochrane risk of bias tool consists of six domains, each may have more than one source of bias application, depending on the subject matter.[7] Our applications were as follows: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel – all outcomes), detection bias (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms, complications and harms outcome data), reporting bias (selective reporting) and other bias. The identification of sources of other bias was left at the reviewers' discretion.

Risk of bias assessments were performed following Cochrane methods [7] and published in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis of data extracted from core reports.

After 12th April 2011, we obtained the appendices of the clinical study reports included in our review. For most clinical study reports we requested, EMA had the protocol, protocol amendments, statistical analysis plan, blank case report forms, and other appendices contained in what Roche terms the second "module" of a full clinical study report (see Appendix 1). However EMA did not possess—and therefore could not provide us with—full clinical study reports with the exception of trial WP16263.[8] For approximately three years Roche had repeatedly refused our requests for full clinical study reports.[9]

In April 2013 in the course of carrying out these new extractions, Roche changed its policy on access to data and pledged to share with us 77 full clinical study reports (www.bmj.com/tamiflu/roche). Fifteen clinical study reports containing 20 trials were included in the analysis of our current review.[10] As we were already in possession of core reports and appendices such as the protocol and statistical analysis plan for the 14

trials in this analysis, the additional data for other clinical study reports provided by Roche does not concern this paper. In the clinical study reports Roche redacted information that they judged to be of “legitimate commercial interest” or present a risk of trial participant re-identification. The redactions did not impede our analyses of risk of bias.

Based on our growing familiarity with clinical study reports, we designed and piloted a data extraction sheet to record how our understanding of the trials changed in light of availability of the additional appendices. We realized that in addition to the standard Cochrane risk of bias elements, we needed to organize the abundant material at our disposal and re-construct a timeline of the trials. We used the Cochrane risk of bias tool [7] to appraise clinical study reports and a data extraction sheet for recording information relevant to this appraisal. We added the following elements to our extraction sheets: date of participant enrollment, unblinding of the trial, protocol for which we had the full text, protocol amendments, statistical analysis plan for which we have the full text (and its amendments), patient consent form, randomization list, and certificate of analysis. Timeline reconstruction allowed us to conceptualise the design and conduct of the trials and appreciate their role in the trial programme with their strengths and limitations. In addition following a timeline allows a judgment to be made on the integrity and temporal sequence of the documents. The finalized extraction sheet is in Appendix 2.

Based on access to full clinical study reports, we carried out our final assessment of risk of bias. These were carried out by a single reviewer, checked by a second with final consensus reached through a face-to-face discussion among the entire group.

Because with full clinical study reports there should be no ambiguity, we only allowed "low" or "high" risk of bias judgments (i.e. no “unclear”). We adopted the position that, unlike a publication which may have page limits, there was no reason a full clinical study report should be missing details necessary for a third party to judge risk of bias. Therefore, when information that would have otherwise allowed us to judge a risk of bias as either "low" or "high" was missing, this would automatically be categorized as “high” risk of bias. This decision to eliminate the “unclear” option when assessing full clinical study reports was made following an initial assessment of the trials, which included “unclear” judgments. Based on earlier peer-review of this paper which suggested we analyze the data had we kept the “unclear” category, we also carried out this post-hoc analysis.

To allow for a comparison of risk of bias judgments based on published reports of trials and risk of bias judgments based on clinical study reports (either core reports alone or full clinical study reports), we used our previous risk of bias judgments for the same trials in the relevant Cochrane reviews that had been based on publications.[11,12]

The extraction and adjudication methods used were the same as those used in our subsequent unified Cochrane review.[6] We used descriptive methods to answer our three questions without the need for formal statistical analysis.

Ethics approval and patient consent were not necessary for this study.

Results

We could only compare risk of bias assessments between core reports and full clinical study reports for the following 14 trials (reported in 10 clinical study reports): M76001; NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978 (Figure 1 and Table 1).

We could not carry out a comparison of risk of bias judgments of journal publications with core reports or full clinical study reports, because our assessments were largely based on secondary publications (notably, the Kaiser et al pooled analysis of ten trials, eight of which were unpublished[13]) rather than primary publications of the trials, and also utilized an outdated risk of bias tool. There were therefore too few studies (3) for which we had distinct risk of bias judgments of primary journal publications (many studies for which we have clinical study reports were and remain unpublished, for example 8 of the 13 trials in adults). In addition, the current Cochrane risk of bias tool was introduced after the production of our review of published articles, making the comparison, had we had the data to undertake it, more difficult to interpret and possibly unfair.

For the comparison of core and full clinical study reports, Table 2 shows that no previous assessment of “high” risk of bias was reclassified as “low” or “unclear” in the presence of more detailed information. Previous assessments of “low” risk of bias were not uncommonly reclassified as “high” bias in the subsequent assessment. While our assessments based on core reports were mostly classified as “low risk of bias” they were reclassified in the opposite direction as “high” risk of bias when our judgments were based on full clinical study reports (Table 2).

A spreadsheet recording all individual risk of bias judgments is available ~~in an~~ online, see supplementa~~l~~ry file 1.

Had we kept the “unclear” risk of bias judgment option when assessing full clinical study reports [10] we would have had 64 “unclear” judgments (see sensitivity analysis in Table 3). The breakdown of these 64 into the various attributes is:

- Attrition bias: symptoms (10); complications (9); safety (15). These were unclear because we do not know the impact of missing symptoms data, the reports contained unclear definitions for secondary complications of influenza, and a seemingly problematic decision tool for the alternative designation of events as either complications or harms, which we called “compliharms” in our Cochrane review.
- Other bias (13) – these are unclear due to the unknown effect of the dehydrocholic acid included in the placebo but not included in the active treatment
- Performance bias (6) – these are unclear due to missing certificates of analysis describing the placebo appearance
- Selection bias (10) – these are unclear due to the missing or unclear randomisation lists meaning we cannot confirm random sequence generation
- Detection bias (1) – unclear due to unknown impact of different coloured placebo caps on outcome assessment

See Tables 3 and 4. Twenty nine percent of previously certain judgments (i.e. “high” or “low” risk of bias) based on core reports became “unclear” with full clinical study reports.

An example of the kind of detail available in full clinical study reports and the importance of the trial timeline in assessing presence of bias, is the observation that of the clinical study reports for the 14 trials, only 1 contained a protocol which predated the beginning of participant enrolment, only 2 had statistical analysis plans which clearly predated participants enrolment and 3 had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding. Completed extraction sheets with risk of bias comparisons and rationales are available on request from the corresponding author.

Discussion

We used the Cochrane six-item risk of bias instrument to assess bias from two different levels of detail of trial reports. Because of unrestricted access to full clinical study reports, we took the view that all information needed to judge risk of bias for each of the six domains of the Cochrane risk of bias should be present. When the information was not available, we judged the corresponding risk of bias element as being “high”. Therefore the availability of full clinical study reports decreased the uncertainty and allowed clearer judgments to be made. Risk of bias previously assessed as “unclear” based on core reports became a more certain "low" or "high" risk of bias.. When the information was not available, our judgments changed because we found gaps in the availability of information and inconsistent information. Whether the full study reports represent an exhaustive and coherent source of trial narrative and data remains unclear.

Throughout our study we were assessing two different types of material within the clinical study reports: those that were created or written prior to patient enrollment (e.g. trial protocols), and those written after (e.g. core reports).

This approach is not possible when assessing trials reported in journal publications, in which articles necessarily reflect post hoc reporting with a far more sparse level of detail. We suggest that when bias is so limiting as to make meta-analysis results unreliable, it either should not be done or a prominent explanation of its clear limitations should be included alongside the meta-analysis. We found the Cochrane risk of bias tool to be difficult to apply to clinical study reports. We think this is not because the tool was constructed to assess journal publications but as with all list-like instruments its use lends itself to a check-list approach (in which each design item is sought and, if found, eliminated from the bias equation rather than with thought and consideration). Similarly, the extraction sheet we assembled needs to be applied with thought and consideration – an approach that does not lend itself to reviewing under time pressure. However more focus should be devoted to bias itself and its effects rather than theoretical *risk* of bias. Many of the variables we found to be important when assessing the trial (e.g. date of trial protocol, date of unblinding, date of participant enrollment) are simply not captured in the risk of bias tool when used in a routine way or to review publications. We were also often unsure how to judge the risk of bias when bias itself can actually or potentially be measured with reviewers’ access to full clinical study reports and individual participant data. If, for

example, the original trial protocol is available, one can judge whether reporting bias occurred. Reviewers need not guess at bias (i.e. make a judgment of “risk”) but can judge bias directly. However even with individual participant data, some forms of bias, such as attrition bias, may still be difficult to quantify, and one can only judge the risk (i.e. potential) of bias. Therefore access to detailed information and participant level data sometimes found in full clinical study reports, provides an opportunity to consider both *actual* as well as *risk of* biases.

Box 1 shows examples of the types of information found in clinical study reports that led to risk of bias assessment changes. While the judgments of “low” or “high” risk of bias may imply certainty, particularly when based on the reading of a full clinical study report, we found ourselves often in lengthy debate and discussion over the proper level of risk of bias before arriving at a consensus. We found the risk of bias judgments themselves to carry a high level of subjectivity, in which different judgments can be justified in different ways. The real strength of the risk of bias tool appears not to be in the final judgments it enables, but rather in the process it helps facilitate: critical assessment of a clinical trial.

Another aspect to emerge is that tools based on publications are designed to detect presence, absence or uncertainty regarding elements in a very restricted number of places in the text. The availability of full clinical study reports allows reviewers to follow consistency across chapters and appendices, creating a need for far more interaction with the text. An example of this active engagement is the cross-checking of active principle and placebo batches used across trials and their connection with a visual description of their properties such as color in a certificate of analysis. For example, once the presence of a differently colored placebo capsule cap in trial WP16263 was identified through the clinical study report’s certificate of analysis, its potential impact on blinding was captured in the Cochrane instrument. The interpretation of such a finding is difficult, as the colors of the active principle and placebo capsule caps are close (ivory and light yellow). However publication-based or core report only based assessments would not have identified the potential differences in color as the descriptions are simply given as “placebo” [14] and “matching placebo” [15] respectively. Reviewing complete clinical study reports and our assessment of bias was very time consuming, necessitating prolonged exchanges including a face-to face meeting given the novelty of what we were doing. This activity though was not as difficult or as time consuming as the reconstruction of trial evidence programmes for oseltamivir, an activity which necessitated a whole time equivalent researcher for 6 months. However because of the threat of reporting bias we can think of no alternative to the use of full clinical study reports.

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents such as randomization lists. Randomization lists appeared to be of two types. The first was a pre-randomization list of random codes with which participants’ IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post-hoc randomization list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not

provided or original codes cannot be matched to patients. Another limitation of our study is the instrument we have developed is for using with clinical study reports, and may not apply to non-industry trials (which may not have a clinical study report).

The background to our use of clinical study reports was our mistrust of journal publications of ~~trials of~~ oseltamivir ~~research~~trials. Many trials were unpublished, and of those published, ~~These~~ we ~~had~~ found and documented examples of reporting bias. At least one trial publication was drafted by an unnamed medical writer~~to be both incomplete, ghost written or simply invisible~~. As evidence of reporting bias in industry trial publication mounts, [8,16–21] we believe Cochrane reviews should increasingly rely on clinical study reports as the basic unit of analysis. ~~Equally s~~Sponsors and researchers both have a responsibility to ~~should~~ make all efforts to make full clinical study reports publicly available. The systematic evaluation of bias or risk of bias remains an essential aspect of evidence synthesis, as it forces reviewers to critically examine trials. However, the current Cochrane risk of bias tool does not sufficiently identify possible faults with study design nor does it help to organize and check coherence of large amounts of information that are found in clinical study reports. Our experience suggests that more detailed extraction sheets that prompt reviewers to consider additional aspects of study may be needed. Until a more appropriate guide is developed, we offer our custom extraction sheets to Cochrane reviewers and others interested in assessing risk of bias using clinical study reports and encourage further development.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

An ethics statement was not required for this work.

~~Contributorship statement.~~ ~~All authors fulfil all three of the ICMJE guidelines for authorship which are 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.~~

Contributorship statement. All authors were involved in the design of the study and the linked Cochrane review. The custom data extraction sheet was designed by TJ, MJ, CH, and PD. All authors extracted the data as described and interpreted it. MJ carried out statistical analyses. TJ wrote the first draft of the manuscript and all authors contributed to subsequent drafts.

Competing interests

Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as 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 FDA). Dr Jefferson was a consultant for IMS Health in 2013 and is currently retained as a scientific advisor to a legal team acting on the drug Tamiflu (oseltamivir, Roche). Dr Jefferson recently had part of his expenses reimbursed for attending the annual (UK) Pharmaceutical Statisticians' Conference.

Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Dr Doshi is an associate editor at The BMJ.

Dr Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and receives fees for editorial and guideline developmental work and royalties from books and in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled "Tamiflu: harmful as was afraid" and "In order to escape from drug-induced encephalopathy". Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.

Data Sharing. The source core reports and clinical study reports can be found at <http://datadryad.org/resource/doi:10.5061/dryad.77471>. A spreadsheet recording all individual risk of bias judgments is available in an online supplemental file to this paper.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports: E3 [Internet]. 1995 [cited 2012 Jul 8]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

2. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open. 2013 Feb 26;3(2):e002496.

3. European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) POLICY/0043 [Internet]. 2010 [cited 2012 May 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf

4. F. Hoffmann-La Roche Ltd. Roche Global Policy on Sharing of Clinical Trials Data [Internet]. 2013 [cited 2013 Jun 19]. Available from: http://roche-trials.com/dataSharingPolicy.action

5. Nisen P, Rockhold F. Access to Patient-Level Data from GlaxoSmithKline Clinical Trials. N Engl J Med. 2013;369(5):475–8.

6. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012;(1):CD008965.

7. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

8. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. BMJ. 2012 Jan 17;344:d7898.

9. Doshi P, Jefferson T, Del Mar C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med. 2012 Apr 10;9(4):e1001201.

10. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

11. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744.

12. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2010;2:CD001265.

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13. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul 28;163(14):1667–72.

14. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents. 2010 May;35(5):461–7.

15. Hoffman-La Roche, Ltd. Clinical Study Report – Protocol WP16263. A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Report No. 1003328. 2001.

16. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.

17. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 2009 Nov 12;361(20):1963–71.

18. Vedula SS, Li T, Dickersin K. Differences in Reporting of Analyses in Internal Company Documents Versus Published Trial Reports: Comparisons in Industry-Sponsored Trials in Off-Label Uses of Gabapentin. PLoS Med. 2013 Jan 29;10(1):e1001378.

19. Rodgers MA, Brown JVE, Heirs MK, Higgins JPT, Mannion RJ, Simmonds MC, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ. 2013;346:f3981.

20. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ. 2010 Oct 12;341(oct12 1):c4737–c4737.

21. Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med. 2013 Oct 8;10(10):e1001526.

22. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev Online. 2009;2:CD001265.

23. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev Online. 2007;(1):CD002744.

Box 1: Examples of risk of bias assessment changes and other concerns

- In trial WV15708, the risk of bias related to allocation concealment went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because the full clinical study report did not report sufficient details about the method of allocation concealment.
- In trial WV15707, the risk of bias related to random sequence generation went from “Unclear” based on core reports to “High” risk of bias based on full clinical study reports because a full description of the randomization procedure was not provided.
- Prophylaxis trials WV15673 and WV15697 are described as "identical" but this could not be verified as we only had one protocol (and the protocol we did have was dated after study completion). In addition, the placebo event rates for influenza infection were very different between the two trials and their pooling, combined with the redaction of center numbers, preventing from being individually added to a meta-analysis. Therefore our assessment of the "Other" risk of bias item changed from "unclear" based on core reports to "high" based on full clinical study reports.
- In the treatment trials WV15819, WV15876, and WV15978, it was difficult to reconcile the total number of hospitalizations despite access to the full clinical study reports. One patient in the placebo arm who was hospitalized according to serious adverse event narratives does not appear in the hospitalizations table and for a separate placebo patient that is listed in the serious adverse event narratives, no hospitalization is described in this narrative but the same patient was hospitalized according to the hospitalizations table. It was therefore unclear how many hospitalizations occurred in the trial, to whom and why.
- In prophylaxis trials WV15673 and WV15697, bias was assessed as low for selective reporting because the intention-to-treat population was described and reported in a table. However when the full clinical study report became available we realised that the original protocol was missing.

	Risk of bias assessment performed based on			
Trial(s)	**Pooled analysis** [13] (2009 Cochrane review[22])	**Journal publication** (2007, 2009 and 2010 Cochrane reviews [12,22,23])	**Core report** (2012 Cochrane review [6])	**Full clinical study report** (2014 Cochrane review [10])
M76001	x		x	x
NV16871			x	x
WV15670		x	x	x
WV15671		x	x	x
WV15707	x		x	x
WV15730	x		x	x
WV15759 WV15871			x	x
WV15799		x	x	x
WV15812 WV15872	x		x	x
WV15819 WV15876 WV15978	x		x	x

Table 1. Risk of bias assessments performed by trial, 2009-2014.

Risk of bias, core reports	**Risk of bias, full clinical study reports**			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	26 (20%)	0 (0%)	0 (0%)	**26 (20%)**
Unclear	28 (22%)	0 (0%)	14 (11%)	**42 (32%)**
Low	34 (26%)	0 (0%)	28 (22%)	**62 (48%)**
Total	**88 (68%)**	**0 (0%)**	**42 (32%)**	**130 (100%)**

Table 2. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports.

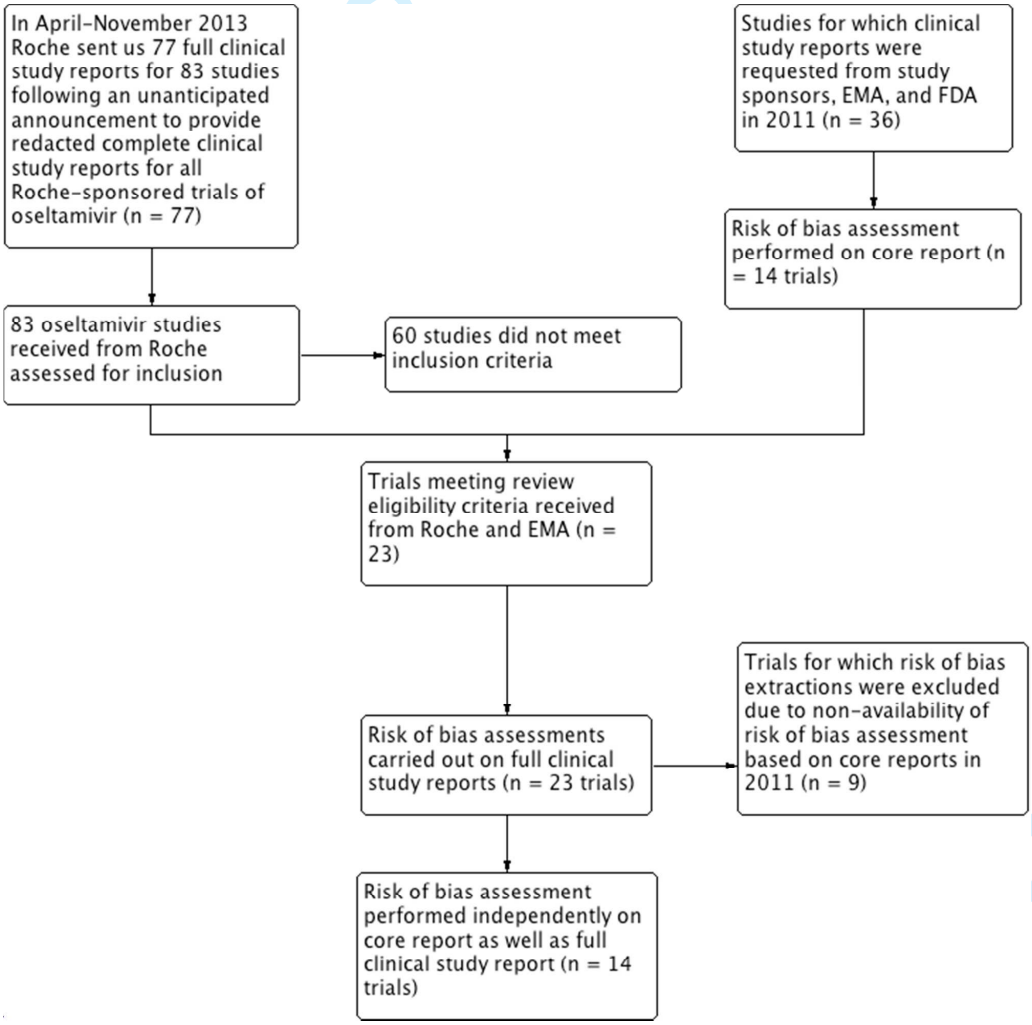
Risk of bias, core reports	**Risk of bias, full clinical study reports**			
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	11 (8%)	15 (12%)	0 (0%)	**26 (20%)**
Unclear	1 (1%)	27 (21%)	14 (11%)	**42 (32%)**
Low	12 (9%)	22 (17%)	28 (22%)	**62 (48%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 3. Change in overall (all elements) risk of bias judgments for 15 core reports of oseltamivir trials compared with full clinical study reports including unclear assessments.

Risk of bias, full clinical	**Risk of bias, full clinical study reports allowing unclear assessments**	

study reports				
	High, n (%)	**Unclear, n (%)**	**Low, n (%)**	**Total, n (%)**
High	24 (18%)	64 (49%)	0 (0%)	**88 (68%)**
Unclear	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
Low	0 (0%)	0 (0%)	42 (32%)	**42 (32%)**
Total	**24 (18%)**	**64 (49%)**	**42 (32%)**	**130 (100%)**

Table 4. Change in overall (all elements) risk of bias judgments for 15 full clinical study reports reports of oseltamivir trials with and without allowing unclear assessments.



~~Figure 1. Study flow diagram~~

Appendix 1. Table of content of an oseltamivir clinical study report, trial WV15799.

Tamiflu® (oseltamivir phosphate)
75mg Capsules, Hard
12 mg/mL Oral Suspension

Roche

5.3.5.4.6 CSR WV15799 (W-144170)

CLINICAL STUDY REPORT MODULES

This report consists of 5 modules.

Those not supplied in this submission are obtainable from the sponsor on request.

MODULE I: CORE REPORT

Background and Rationale
Objectives
Materials and Methods
Efficacy Results
Safety Results
Discussion
Conclusion
Appendices

MODULE II: STUDY DOCUMENTS

Protocol and Amendment History
Blank Case Report Form (CRF)
Subject Information Sheet and Consent Form
Glossaries of Original and Preferred Terms
Randomization List
Reporting Analysis Plan (RAP)
Certificates of Analysis
List of Investigators
List of Ethics Committee

MODULE III: LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA

MODULE IV: LISTINGS OF SAFETY DATA

MODULE V: STATISTICAL REPORT AND APPENDICES

Statistical Analysis
Efficacy Results

Appendix 2. Mapping and extraction tool for oseltamivir clinical study report (CSR) Module 2 elements to Cochrane Characteristics of Included Studies elements

Mapping Tamiflu CSR Module 2 elements to Cochrane Characteristics of Included Studies elements

Aim: To identify sections of the Clinical Study Reports (CSRs) Module 2 (defined as what Roche calls "Module 2") which may improve understanding of the content of the Cochrane included studies table (CIST).

Drug:	Oseltamivir (Tamiflu)
CSR for trial(s):	
Reviewer:	
Date(s) of extraction:	

Notes:

1. **Do not remove this notice**
2. **Do not merge cells in the tables (Merged cells wreak havoc in collating answers in a spreadsheet)**
3. **Do not copy-paste images from the CSR**

Trial Summary

Trial summary given in…	Trial summary
CSR	(*Short (2-3) sentence description of the trial as given in the CSR – most likely in the Synopsis section.*)
A159 (January 2012)	(*Copy and/or assemble this from the Characteristics of Included Studies table in the A159 review published in January 2012.*)
Your own words, after extracting M2	(*Write a new trial summary that is accurate based on your understanding of the trial after reading M2.*)

Risk of bias

Bias	A159 (Jan 2012) judgment	A159 (Jan 2012) support for judgment	Reviewer's judgment (post M2)	Support for judgment
Random sequence generation (selection bias)				
Allocation				

concealment (selection bias)				
Incomplete outcome data (attrition bias), symptoms				
Incomplete outcome data (attrition bias), complications of influenza				
Incomplete outcome data (attrition bias), safety data				
Selective reporting (reporting bias), other bias				
Other bias				
Blinding of participants and personnel (performance bias), all outcomes				
Blinding of outcome assessment (detection bias), all outcomes				

Trial timeline

Serial	Timeline element	Date	Version (if a version name/number is given)	Page (PDF page no.) where item can be found
A	Patient enrollment dates			
B	Unblinding of the trial			
C	Protocol for which we have the full text (if we have multiple versions in full text, record all dates and versions)			
D	Protocol amendments (list all amendments with dates and their version stamp)			
E	Statistical Analysis Plan for which we have the full text (if we have multiple versions in full text, record all dates and versions)			

F	SAP amendments (list all amendments with dates and their version stamp)			
G	Patient consent form			
H	Randomization list			
I	Certificate of Analysis			

Reviewing sequence (write answers in each box)

Serial	Cochrane Characteristics of Included Studies	Check these M2 elements with care:	Is M1 reporting consistent with M2? Yes – No – Unclear (choose one)	If the answer is no then record the difference
1	METHODS			
1a	○ Study Design	RPS		
1b	○ Location, number of centers	RPS LIESA		
1c	○ Duration of study	RPS		
2	PARTICIPANTS			
2a	○ Number screened	-	LEAVE BLANK UNLESS NEEDED	LEAVE BLANK UNLESS NEEDED
2b	○ Number randomized	-		
2c	○ Number completed	-		
2d	○ Number analysed	-		
2e	○ Male/Female ratio	-		
2f	○ Mean age	-		
2g	○ Baseline details	-		
2h	○ Inclusion criteria	RPS		
2i	○ Exclusion criteria	RPS		
2j	○ Definition of patient populations for analysis	RPS RAP		
3	INTERVENTIONS			

3a	○ Intervention	RPS CA RAP		
3b	○ Control	RPS CA RAP		
3c	○ Treatment period	RPS RAP FUC		
3d	○ Treatment duration	RPS RAP FUC		
3e	○ Follow up (in days)	RPS RAP FUC		
3f	○ Co-interventions	RPS RAP		
4	OUTCOMES			
4a	○ Primary outcome	RPS RAP CRF Note: ensure CRF can capture relevant info		
4b	○ Secondary outcomes	RPS RAP CRF Note: ensure CRF can capture relevant info		
5	NOTES			Make any other points you wish here
6	RISK OF BIAS			
6a	○ Random sequence generation (selection bias)	RPS RL		
6b	○ Allocation concealment (selection bias)	RPS		
6c	○ Incomplete outcome data (attrition bias)	RPS IC Note: IC may contain		

		details that suggest possible influence on retention or attrition		
6d	○ Selective reporting (reporting bias)	RPS IC LIESA Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	○ Other bias	RPS		
6f	○ Blinding of participants and personnel (performanc e bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR	Are the intervention and control identical in all but the active principle?	
6g	○ Blinding of outcome assessment (detection bias)	RPS CA Note: ensure CA supports description of placebo and active elsewhere in CSR		

CA = Certificate of Analysis
CRF = Case Report Form(s)
FUC = Follow up cards/Diary cards
IC = Informed Consent and participant contract
LIESA = Lists of Investigators, IRB, EC and Site Addresses
RAP = Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan (SAP))
RL = Randomisation List
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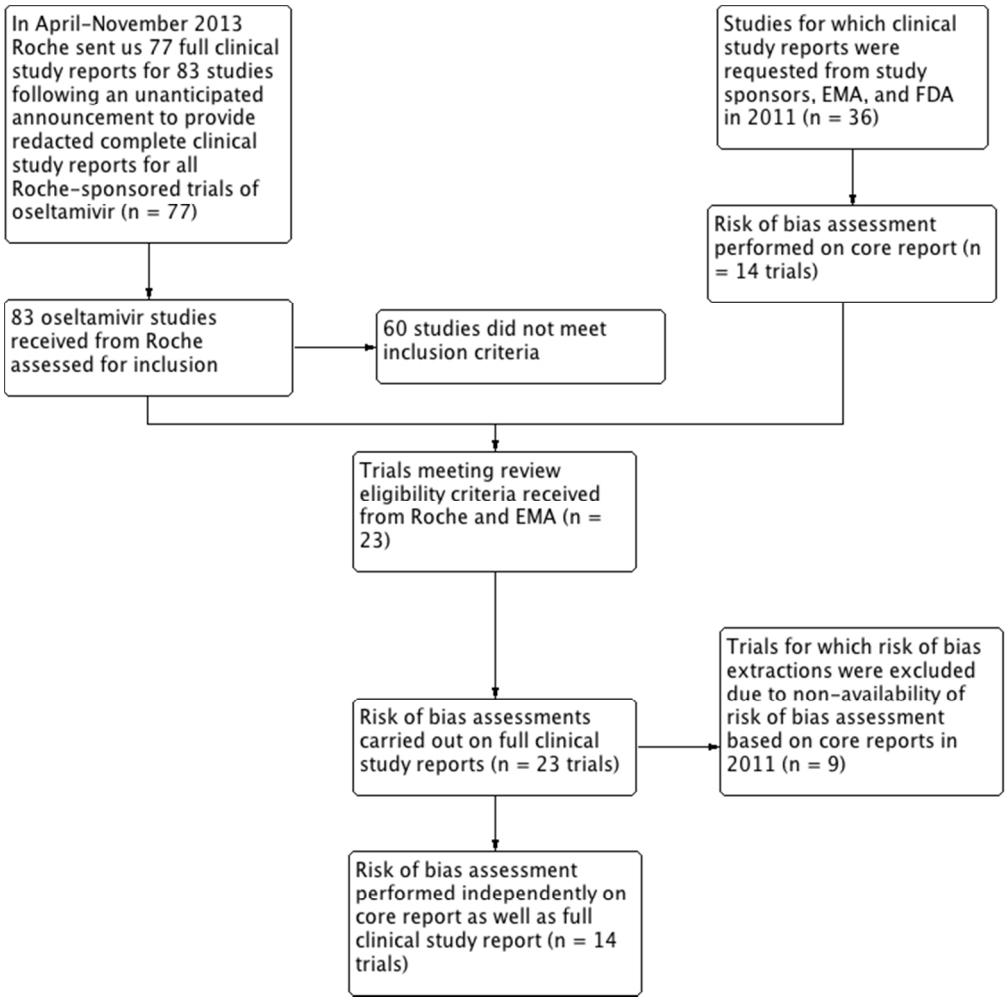

Figure 1 Flow chart
256x253mm (72 x 72 DPI)

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Roche

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Incomplete outcome data (attrition bias), complications of influenza				
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Selective reporting (reporting bias), other bias				
Other bias				
Blinding of participants and personnel (performance bias), all outcomes				
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2f	○ Mean age	-		
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6	RISK OF BIAS			
6a	○ Random sequence generation (selection bias)	RPS RL		
6b	○ Allocation concealment (selection bias)	RPS		
6c	○ Incomplete outcome data (attrition bias)	RPS IC Note: IC may contain		

		details that suggest possible influence on retention or attrition		
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Prepared August 22, 2014

Instructions: Unfortunately, the manuscript system did not allow for Microsoft Excel files as supplementary files, only Microsoft Word. Therefore we have prepared this file to share our underlying dataset. To work with the data below, it may be easiest to select the table below and copy all values into a spreadsheet program e.g. Excel.

Trial ID	ROB element	2012 assessment	2012 rationale
M76001	Random sequence generation (selection bias)	Low	
M76001	Allocation concealment (selection bias)	Low	
M76001	Incomplete outcome data (attrition bias), symptoms	Low	
M76001	Incomplete outcome data (attrition bias), complications of influenza	Unclear	Unclear how complications of influenza were d
M76001	A159: Incomplete outcome data (attrition bias) safety		
M76001	Safety data	Low	
M76001	A159: Selective reporting (reporting bias)	Low	
M76001	A159: Other bias		
M76001	A159: Blinding of participants and personnel (performance bias)		
M76001	All outcomes	Unclear	Capsule size, but no details of colour or taste or c
M76001	A159: Blinding of outcome assessment (detection bias)		
M76001	All outcomes	Low	
NV16871	Random sequence generation (selection bias)	Low	
NV16871	Allocation concealment (selection bias)	Low	

NV16871	Incomplete outcome data (attrition bias), symptoms	Low	
NV16871	Incomplete outcome data (attrition bias), complications of influenza	Low	
NV16871	A159: Incomplete outcome data (attrition bias)		
NV16871	Safety data	Low	
NV16871	A159: Selective reporting (reporting bias)		
NV16871	A159: Other bias		
NV16871	A159: Blinding of participants and personnel (performance bias)		
NV16871	All outcomes	Unclear	Placebo colour/taste/contents not clear
NV16871	A159: Blinding of outcome assessment (detection bias)		
NV16871	All outcomes	Low	
WP16263	Random sequence generation (selection bias)	Unclear	Unclear risk Described as randomised; procedure
WV15670	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating r "The randomisation numbers were generated by inc., Princeton, NJ, USA)."
WV15670	Allocation concealment (selection bias)	Low	"The investigator telephoned the centre to report The randomization number was then supplied by system (IVRS). The investigator entered the rand
WV15670	Incomplete outcome data (attrition bias), symptoms	High	Available data analyzed by ITTI population and no
WV15670	Incomplete outcome data (attrition bias),	High	Possible effect of oseltamivir on antibody product complications in the infected subpopulation non-

	complications of influenza		
WV15670	Incomplete outcome data (attrition bias), safety data	Low	Based on all participants irrespective of compliance
WV15670	Selective reporting (reporting bias), other bias	High	Outcomes of primary interest for the ITT populati
WV15670	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage no "In order to maintain blinding, each subject had 2 administered from each bottle twice per day at ap the first (day 1) visit
WV15670	Blinding of participants and personnel (performance bias), all outcomes	Low	Each bottle was labelled with the subject number placebo. Those subjects receiving 75 mg bid receiv matching capsule containing placebo from the bott received one capsule containing 75 mg active dru "No open key to the randomisation code was avai
WV15670	Blinding of outcome assessment (detection bias), all outcomes	Low	Roche Headquarters. In the event of a medical em necessary to properly manage the subject, by con The blinding was not required to be broken for an
WV15670	Random sequence	Unclear	Described as randomised; procedure generating

1	generation (selection bias)		randomisations schedule not available "Randomisation was conducted by a central rando The investigator /study coordinator telephoned t the subjects initials, date of birth and smoking his randomisations
WV1567 1	Allocation concealment (selection bias)	Low	number was entered in the appropriate place on the subject's Case Report Form by th in
WV1567 1	Incomplete outcome data (attrition bias), symptoms	Low	Data from study participants without influenza were available for symptom relief
WV1567 1	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
WV1567 1	Incomplete outcome data (attrition bias), safety data	Low	Based on all participants irrespective of compliancewith treatment or infection status
WV1567 1	Selective reporting (reporting bias), other bias	Low	Outcomes of primary interest for the ITT population available in the CONSORT reconstr
WV1567 1	Other bias	High	Placebo contained dehydrocholic acid Matching placebo used "In order to maintain the double blind nature of the study, subjects received 2 capsules twice daily for all treatments."
WV1567 1	Blinding of participants and personnel (performance bias), all outcomes	Low	"The identification number was added by the investigator at the time of randomisations "No open key to the code was available at the Study Center..."
WV1567 1	Blinding of outcome assessment (detection bias), all outcomes	Low	"The identification number was added by the investigator at the time of randomisations "No open key to the code was available at the Study Center, to the Monitors, Statistician or at Gilead/Roche Headquarters"
WV1567 3 WV1569 7	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating r
WV1567 3 WV1569	Allocation concealment (selection bias)	Unclear	Inadequate information available to ascertain con

7			
WV15673			
WV15697	Incomplete outcome data (attrition bias), symptoms	Low	Not applicable to the study design (prophylaxis)
WV15673	Incomplete outcome data (attrition bias), complications of		Possible effect of oseltamivir on antibody product
WV15697	influenza	High	complications in the infected subpopulation non-i
WV15673	A159: Incomplete outcome data (attrition		
WV15697	bias)		
7	Safety data	Low	Based on all randomised participants
WV15673			
WV15697	A159: Selective reporting (reporting		
7	bias)	Low	Outcomes of primary interest for the ITT populati
WV15673			
WV15697			
7	A159: Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage
WV15673	A159: Blinding of participants and personnel (performance		
WV15697	bias)		
7	All outcomes	Unclear	Capsule size, but no details of colour or taste or c
WV15673	A159: Blinding of outcome assessment		
WV15697	(detection bias)		
7	All outcomes	Unclear	Inadequate information available to ascertain wh
WV15707	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating r
WV15707	Allocation concealment (selection bias)	Low	"Randomization was performed by a central rand the subject's date of birth, vaccination status and randomisation centre."
WV15707	Incomplete outcome data (attrition bias), symptoms	High	Available data analyzed by ITTI population and no
WV15707	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody product complications in the infected subpopulation non-i

WV15707	A159: Incomplete outcome data (attrition bias) Safety data	Low	Based on all randomised participants
WV15707	A159: Selective reporting (reporting bias)	High	Outcomes of primary interest for the ITT populati
WV15707	A159: Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage no
WV15707	A159: Blinding of participants and personnel (performance bias) All outcomes	Low	Presentation of placebo described as identical
WV15707	A159: Blinding of outcome assessment (detection bias) All outcomes	Unclear	Inadequate information available to ascertain wh
WV15708	Random sequence generation (selection bias)	Unclear	Randomization numbers generated by Roche, Erasmushogeschool
WV15708	Allocation concealment (selection bias)	Unclear	Insufficient details given
WV15708	Incomplete outcome data (attrition bias), symptoms	Low	Outcomes available on all patients who complete
WV15708	Incomplete outcome data (attrition bias), complications of influenza	Low	
WV15708	A159: Incomplete outcome data (attrition bias) Safety data	Low	Outcome data on all patients provided.
WV15708	A159: Selective reporting (reporting bias)	Low	Outcome data reported.
WV15708	A159: Other bias	Unclear	Placebo contents and colour and similarity to acti, could not analyze for primary outcome of efficacy
WV15708	A159: Blinding of participants and personnel (performance bias) All outcomes	Low	

WV15708	A159: Blinding of outcome assessment (detection bias) All outcomes	Low	Outcome assessors were blind
WV15730	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV15730	Allocation concealment (selection bias)	Low	"Randomization was performed by a central randomisations service. The investigator telephoned the centre to report the subject's data number was then supplied by the randomisationsn
WV15730	Incomplete outcome data (attrition bias), symptoms	High	Available data analysed by ITTI population and not ITT
WV15730	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
WV15730	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
WV15730	Selective reporting (reporting bias), other bias	High	Outcomes of primary interest for the ITT population not made available to the review and Erasmushogeschool .
WV15730	Other bias	High	Placebo capsule contained dehydrocholic acid
WV15730	Blinding of participants and personnel (performance bias), all outcomes	Low	Matching placebo.
WV15730	Blinding of outcome assessment (detection bias), all outcomes	Low	"No open key to the code was available at the study centre, to the monitors, statistician or at Roche Headquarters. In the event of a medical emergency the blinding was to be broken if considered absolutely mandatory to properly manage the patient
WV15758	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV15758	Allocation concealment (selection bias)	Low	"Randomization was conducted by a central randomisations service, ICTI (Interactive

			Clinical Technologies Inc., Princeton, NJ). The investigator telephoned the centre to report the subject's date of birth, sex, a centre in the form of a message on an interactive response system (IVRS). The investigator entered the randomisations number in the appropriate place on the case report form. The subject randomisations numbers were allocated sequentially within a stratum in the order in which subjects were enrolled."
WV15758	Incomplete outcome data (attrition bias), symptoms	Low	Data available for both influenza infected and non-infected study populations
WV15758	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable be
WV15758	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomized patients
WV15758	Selective reporting (reporting bias), other bias	Low	Outcomes of primary interest to the review for ITT population available in the CONSORT-based extraction reconstruction
WV15758	Other bias	Unclear	Unable to ascertain placebo capsule contents
WV15758	Blinding of participants and personnel (performance bias), all outcomes	Low	"No open key to the code was available at the study centre..."
WV15758	Blinding of outcome assessment (detection bias), all outcomes	Low	"No open key to the code was available (...) to the Roche monitors, statisticians or at Roche Headquarters."
WV15759 WV15871	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV15759 WV15871	Allocation concealment (selection bias)	Low	The subject randomizations numbers will be generated by Roche or its designee and incorp Randomization will be conducted by a central randomization service by telephone.
WV15759 WV15871	Incomplete outcome data (attrition bias), symptoms	Unclear	Insufficient information was available to ascertain populations for analysis and judge risk of bias

WV15759 WV15871	Incomplete outcome data (attrition bias), complications of influenza	Unclear	Insufficient information was available to ascertain populations for analysis and judge risk of bias
WV15759 WV15871	Incomplete outcome data (attrition bias), safety data	Unclear	Insufficient information was available to ascertain populations for analysis and judge risk of bias
WV15759 WV15871	Selective reporting (reporting bias), other bias	High	No outcome data were provided in the study CONSORT-based extraction reconstruction
WV15759 WV15871	Other bias	High	Placebo capsule contained dehydrocholic acid
WV15759 WV15871	Blinding of participants and personnel (performance bias), all outcomes	Low	Matching placebo
WV15759 WV15871	Blinding of outcome assessment (detection bias), all outcomes	Unclear	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment
WV15799	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV15799	Allocation concealment (selection bias)	Unclear	Inadequate information available to ascertain concealment of allocation
WV15799	Incomplete outcome data (attrition bias), symptoms	Low	Not applicable to the study design (prophylaxis)
WV15799	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
WV15799	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
WV15799	Selective reporting (reporting bias), other bias	High	Outcome data for ITT population were not available to the review authors

WV15799	Other bias	Unclear	No information available on placebo contents
WV15799	Blinding of participants and personnel (performance bias), all outcomes	Unclear	Inadequate information available to ascertain presentation of placebo capsules
WV15799	Blinding of outcome assessment (detection bias), all outcomes	Unclear	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment
WV15812 WV15872	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating r "The randomisation numbers were generated by inc., Princeton, NJ, USA)."
WV15812 WV15872	Allocation concealment (selection bias)	Low	"The investigator telephoned the centre to report The randomization number was then supplied by system (IVRS). The investigator entered the rand
WV15812 WV15872	Incomplete outcome data (attrition bias), symptoms	High	Available data analyzed by ITTI population and
WV15812 WV15872	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody product complications in the infected subpopulation non-
WV15812 WV15872	Incomplete outcome data (attrition bias), safety data	Low	Based on all participants irrespective of compli
WV15812 WV15872	Selective reporting (reporting bias), other bias	High	Outcomes of primary interest for the ITT populati
WV15812 WV15872	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage no
WV15812 WV15872	Blinding of participants and personnel (performance bias), all outcomes	Low	Matching placebo described
WV15812	Blinding of outcome	Unclear	Inadequate information available to ascertain wh

2 WV15872 WV15819 WV15876 WV15978 WV15819 WV15876 WV15978 WV15819 WV15876 WV15978 WV15819 WV15876 WV15978 WV15819 WV15876 WV15978 WV15819	assessment (detection bias), all outcomes		of treatment group assignment
	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
	Allocation concealment (selection bias)	Low	“Randomization was conducted by a central randomisations service via telephone. The investigator or study coordinator telephoned vaccination status and history of COAD, and the tr number was then supplied by the centre. The ran in the appropriate place on the subject’s Case Rep
	Incomplete outcome data (attrition bias), symptoms	Low	Available data analysed for both by ITTI and ITT populations
	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
	Selective reporting (reporting bias), other bias	Low	Outcomes of primary interest to the review are available in the CONSORT-based extractions reconstruction
	Other bias	High	Placebo capsule contained dehydrocholic acid

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WV15819			
WV15876	Blinding of participants and personnel (performance bias), all outcomes	Low	Matching placebo described
WV15819			
WV15876	Blinding of outcome assessment (detection bias), all outcomes	Low	"No open key to the code was available at the study centres, to the monitors, statistician or at Roche headquarters. In the event of a medica mandatory to properly manage the subject, by co the randomisations centre."
WV15825	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating r
WV15825	Allocation concealment (selection bias)	Unclear	Inadequate information available to ascertain
WV15825	Incomplete outcome data (attrition bias), symptoms	Low	Not applicable to the study design (prophylaxi
WV15825	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody product complications in the infected subpopulation non-
WV15825	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
WV15825	Selective reporting (reporting bias)	High	Outcome data relating to complications were not
WV15825	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage no
WV15825	Blinding of participants and personnel (performance bias), all outcomes	Unclear	
WV15825	Blinding of outcome assessment (detection bias), all outcomes	Unclear	