

# BMJ Open

## Risk of bias in industry-funded oseltamivir trials: comparison of journal publications and unpublished clinical study reports

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005253
Article Type:	Research
Date Submitted by the Author:	14-Mar-2014
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<b>Primary Subject Heading</b>:	Evidence based practice
Secondary Subject Heading:	Research methods, Qualitative research
Keywords:	STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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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 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.

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**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

## 70 Introduction

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

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

80 Clinical study reports are considered the most exhaustive summaries of randomized  
81 controlled trials of pharmaceuticals. Clinical study reports are highly structured and  
82 detailed documents that follow an outline format agreed between regulators and  
83 manufacturers in 1995 described in the ICH E3 document.[1,2] Recent transparency  
84 policies adopted by the European Medicines Agency,[3] as well as recent announcements  
85 by some pharmaceutical companies to make clinical study reports more readily available  
86 [4,5] suggest that clinical study reports may increasingly be incorporated into systematic  
87 reviews and other forms of evidence synthesis.

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

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

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

108 We aimed to investigate whether and how the level of detail in reporting a trial affects  
109 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](http://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 “compli harms” 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



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

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

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

## 241 Discussion

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

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

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

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3 272 situation, it seems to make little sense to judge the risk (i.e. potential) of attrition bias, but  
4 273 this is what the Cochrane tool asks us to do.  
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6 274 Box 1 shows examples of the types of information found in clinical study reports that led to  
7 275 risk of bias assessment changes. While the judgments of “low” or “high” risk of bias may  
8 276 portray certainty, particularly when based on the reading of a full clinical study report, we  
9 277 found ourselves often in lengthy debate and discussion over the proper level of risk of bias  
10 278 before arriving at a consensus. We found the risk of bias judgments themselves to carry a  
11 279 great amount of subjectivity, in which different judgments can be justified in different ways.  
12 280 The real strength of the risk of bias tool appears not to be in the final judgments it enables,  
13 281 but rather in the process it helps facilitate: critical assessment of a clinical trial.  
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17 282 Another aspect that became obvious is that tools based on publications are designed to  
18 283 detect presence, absence or uncertainty regarding elements in a very restricted number of  
19 284 places in the text. The availability of full clinical study reports allows reviewers to follow  
20 285 consistency across chapters and appendices, creating a need for far more interaction with  
21 286 the text. An example of this active engagement is the cross-checking of active principle  
22 287 and placebo batches used across trials and their connection with a visual description of  
23 288 their properties such as color in a certificate of analysis. For example, once the presence  
24 289 of a differently colored placebo capsule cap in trial WP16263 was identified through the  
25 290 clinical study report’s certificate of analysis, its potential impact on blinding was captured in  
26 291 the Cochrane instrument. The interpretation of such a finding is open to question, as the  
27 292 colors of the active principle and placebo capsule caps are close (ivory and light yellow).  
28 293 However publication-based or core report only based assessments would not have  
29 294 identified the potential differences in color as the descriptions given are “placebo” [13] and  
30 295 “matching placebo” [14] respectively.  
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36 296 The main limitation of our study is our relative inexperience in dealing with large quantities  
37 297 of information and our lack of familiarity with certain trial documents such as randomization  
38 298 lists. Randomization lists appeared to be of two types. The first was a pre-randomization  
39 299 list of random codes with which participants’ IDs cannot be matched with the participant  
40 300 IDs used within other sections of the clinical study report. The second was a post-hoc  
41 301 randomization list to which individual participants can be matched but the original  
42 302 generated codes are not shown. In both cases the truly random generation of the  
43 303 sequence could not be properly assessed because either the original codes are not  
44 304 provided or original codes cannot be matched to patients. Another limitation of our study is  
45 305 the instrument we have developed is for using with clinical study reports, and may not  
46 306 apply to non-industry trials (which may not have a clinical study report).  
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51 307 As evidence of reporting bias in industry trial publication mounts, [8,15–20] we believe  
52 308 Cochrane reviews should increasingly rely on clinical study reports as the basic unit of  
53 309 analysis. The systematic evaluation of bias or risk of bias remains an essential aspect of  
54 310 evidence synthesis, as it forces reviewers to critically examine trials. However, the current  
55 311 Cochrane risk of bias tool is not adequate for the task as it does not reliably identify all  
56 312 types of important biases nor does it organize and check coherence of large amounts of  
57 313 information that are found in clinical study reports. Until a more appropriate instrument is  
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developed, we propose our tool as a possible interim measure to be used and adapted across a wide range of clinical study reports.

**Acknowledgements.** We thank Toby Lasserson for providing advice and an independent check of our risk of bias judgments. 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 [www.hta.ac.uk/2352](http://www.hta.ac.uk/2352). 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 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

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3 350 in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a  
4 351 private donor (for support of the editorial base of the Cochrane ARI Group).  
5  
6 352 Dr Hama receives royalties from two books published in 2008 titled “Tamiflu: harmful as  
7 353 was afraid” and “In order to escape from drug-induced encephalopathy”. Dr Hama  
8 354 provided scientific opinions and expert testimony on 11 adverse reaction cases related to  
9 355 oseltamivir and gefitinib.  
10  
11 356 Drs Jefferson, Jones, Heneghan, Doshi, Del Mar, Thompson and Hama are co-recipients  
12 357 of a UK National Institute for Health Research grant (HTA - 10/80/01 Update and  
13 358 amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and  
14 359 treating influenza in healthy adults and children - <http://www.hta.ac.uk/2352>).  
15  
16 360 Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.  
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**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.

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

16

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



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

466  
467

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

**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	<ul style="list-style-type: none"><li>○ Selective reporting (reporting bias)</li></ul>	RPS IC LIESA  Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	<ul style="list-style-type: none"><li>○ Other bias</li></ul>	RPS		
6f	<ul style="list-style-type: none"><li>○ Blinding of participants and personnel (performance bias)</li></ul>	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	<ul style="list-style-type: none"><li>○ Blinding of outcome assessment (detection bias)</li></ul>	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.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005253.R1
Article Type:	Research
Date Submitted by the Author:	10-Jun-2014
Complete List of Authors:	Jefferson, Tom; The Cochrane Collaboration, Cochrane ARI Group Jones, Mark; University of Queensland, School of Population Health Doshi, Peter; University of Maryland, School of Pharmacy Del Mar, Chris; Bond University, Faculty of Health Sciences and Medicine Hama, Rokuro; Japan Institute of Pharmacovigilance, Director Thompson, Matthew; University of Oxford, Department of Primary Care Health Sciences Onakpoya, Igho; University of Oxford, Primary Care Health Sciences Heneghan, Carl; Oxford University, Primary Health Care
<b>Primary Subject Heading</b>:	Evidence based practice
Secondary Subject Heading:	Research methods, Qualitative research
Keywords:	STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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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

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**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



## 71 Introduction

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

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

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

89 Although there is some variation in the structure and content of clinical study reports, they  
 90 are usually composed of a core report of the trial and appendices. A core report (sections  
 91 1-15 of the ICH E3 document) is structured in Introduction, Methods Results And  
 92 Discussion (IMRAD) style. The numerous appendices (section 16 of ICH E3) contain  
 93 important supplementary data needed to understand and interpret the trial, its context and  
 94 history.[1,2] These appendices include such documents as the trial protocol, protocol  
 95 amendments, statistical analysis plan, blank case report forms, certificates of analysis,  
 96 randomization lists, and consent forms. For the purposes of this paper the core report plus  
 97 all its appendices will be known as the full clinical study report. (See Appendix 1 for the  
 98 table of contents of a typical oseltamivir clinical study report and  
 99 <http://dx.doi.org/10.5061/dryad.77471> for free download of all the clinical study reports  
 100 used in our review and featured in this paper. The core report was known as Module 1 in  
 101 oseltamivir clinical study reports, and appendices were found in Modules 2-5.) Core  
 102 reports and full clinical study reports theoretically can help reduce uncertainty in judging  
 103 risk of bias.

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

110 Our overall aim was to investigate whether the level of detail contained in reports of trials  
 111 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 12<sup>th</sup> 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](http://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

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

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

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

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

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

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

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

## 195 Results

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3 196 We could only compare risk of bias assessments between core reports and full clinical  
4 197 study reports for the following 14 trials (reported in 10 clinical study reports): M76001;  
5 198 NV16871; WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799;  
6 199 WV15812/WV15872; WV15819/WV15876/WV15978 (Figure 1 and Table 1).  
7  
8  
9 200 We could not carry out a comparison of risk of bias judgments of journal publications with  
10 201 core reports or full clinical study reports, because our assessments were largely based on  
11 202 secondary publications (notably, the Kaiser et al pooled analysis of ten trials, eight of  
12 203 which were unpublished[13]) rather than primary publications of the trials, and also utilized  
13 204 an outdated risk of bias tool. There were therefore too few studies for which we had  
14 205 distinct risk of bias judgments of primary journal publications (many studies for which we  
15 206 have clinical study reports were and remain unpublished, for example 8 of the 13 trials in  
16 207 adults). In addition, the current Cochrane risk of bias tool was introduced after the  
17 208 production of our review of published articles, making the comparison, had we had the  
18 209 data to undertake it, more difficult to interpret and possibly unfair.  
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22 210 For the comparison of core and full clinical study reports, Table 2 shows that no previous  
23 211 assessment of “high” risk of bias was reclassified as “low” or “unclear” in the presence of  
24 212 more detailed information. Previous assessments of “low” risk of bias were not  
25 213 uncommonly reclassified as “high” bias in the subsequent assessment. While our  
26 214 assessments based on core reports were mostly classified as “low risk of bias” they were  
27 215 reclassified in the opposite direction as “high” risk of bias when our judgments were based  
28 216 on full clinical study reports (Table 2).  
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32 217 Had we kept the “unclear” risk of bias judgment option when assessing full clinical study  
33 218 reports [10] we would have had 64 “unclear” judgments (see sensitivity analysis in Table  
34 219 3). The breakdown of these 64 into the various attributes is:  
35  
36  
37 220 • Attrition bias: symptoms (10); complications (9); safety (15). These were unclear  
38 221 because we do not know the impact of missing symptoms data, the reports  
39 222 contained unclear definitions for secondary complications of influenza, and a  
40 223 seemingly problematic decision tool for the alternative designation of events as  
41 224 either complications or harms, which we called “compliharms” in our Cochrane  
42 225 review.  
43 226 • Other bias (13) – these are unclear due to the unknown effect of the dehydrocholic  
44 227 acid included in the placebo but not included in the active treatment  
45 228 • Performance bias (6) – these are unclear due to missing certificates of analysis  
46 229 describing the placebo appearance  
47 230 • Selection bias (10) – these are unclear due to the missing or unclear randomisation  
48 231 lists meaning we cannot confirm random sequence generation  
49 232 • Detection bias (1) – unclear due to unknown impact of different coloured placebo  
50 233 caps on outcome assessment  
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55 234 See Tables 3 and 4. Twenty nine percent of previously certain judgments (i.e. “high” or  
56 235 “low” risk of bias) based on core reports became “unclear” with full clinical study reports.  
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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

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3 278 attrition bias, may still be difficult to quantify, and one can only judge the risk (i.e. potential)  
4 279 of bias. Therefore access to detailed information and participant level data sometimes  
5 280 found in full clinical study reports, provides an opportunity to consider both *actual* as well  
6 281 as *risk of biases*.

8  
9 282 Box 1 shows examples of the types of information found in clinical study reports that led to  
10 283 risk of bias assessment changes. While the judgments of “low” or “high” risk of bias may  
11 284 imply certainty, particularly when based on the reading of a full clinical study report, we  
12 285 found ourselves often in lengthy debate and discussion over the proper level of risk of bias  
13 286 before arriving at a consensus. We found the risk of bias judgments themselves to carry a  
14 287 high level of subjectivity, in which different judgments can be justified in different ways.  
15 288 The real strength of the risk of bias tool appears not to be in the final judgments it enables,  
16 289 but rather in the process it helps facilitate: critical assessment of a clinical trial.

19  
20 290 Another aspect to emerge is that tools based on publications are designed to detect  
21 291 presence, absence or uncertainty regarding elements in a very restricted number of places  
22 292 in the text. The availability of full clinical study reports allows reviewers to follow  
23 293 consistency across chapters and appendices, creating a need for far more interaction with  
24 294 the text. An example of this active engagement is the cross-checking of active principle  
25 295 and placebo batches used across trials and their connection with a visual description of  
26 296 their properties such as color in a certificate of analysis. For example, once the presence  
27 297 of a differently colored placebo capsule cap in trial WP16263 was identified through the  
28 298 clinical study report’s certificate of analysis, its potential impact on blinding was captured in  
29 299 the Cochrane instrument. The interpretation of such a finding is difficult, as the colors of  
30 300 the active principle and placebo capsule caps are close (ivory and light yellow). However  
31 301 publication-based or core report only based assessments would not have identified the  
32 302 potential differences in color as the descriptions are simply given as “placebo” [14] and  
33 303 “matching placebo” [15] respectively. Reviewing complete clinical study reports and our  
34 304 assessment of bias was very time consuming, necessitating prolonged exchanges  
35 305 including a face-to face meeting given the novelty of what we were doing. This activity  
36 306 though was not as difficult or as time consuming as the reconstruction of trial evidence  
37 307 programmes for oseltamivir, an activity which necessitated a whole time equivalent  
38 308 researcher for 6 months. However because of the threat of reporting bias we can think of  
39 309 no alternative to the use of full clinical study reports.

46 310 The main limitation of our study is our relative inexperience in dealing with large quantities  
47 311 of information and our lack of familiarity with certain trial documents such as randomization  
48 312 lists. Randomization lists appeared to be of two types. The first was a pre-randomization  
49 313 list of random codes with which participants’ IDs cannot be matched with the participant  
50 314 IDs used within other sections of the clinical study report. The second was a post-hoc  
51 315 randomization list to which individual participants can be matched but the original  
52 316 generated codes are not shown. In both cases the truly random generation of the  
53 317 sequence could not be properly assessed because either the original codes are not  
54 318 provided or original codes cannot be matched to patients. Another limitation of our study is  
55 319 the instrument we have developed is for using with clinical study reports, and may not  
56 320 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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**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 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

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

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

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

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

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**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.



Trial(s)	Risk of bias assessment performed based on			
	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			Total, n (%)
	High, n (%)	Unclear, n (%)	Low, 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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For peer review only

**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 bias ~~judgements~~ and allowed ~~definitive~~ 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 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 sheet instrument we have developed is for use with clinical study reports, and may not apply to non-industry trials because 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 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~~<sup>typically</sup> 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~~<sup>main</sup> 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~~and 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-see Appendix 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 this paper).~~ The core report was known as Module 1 in oseltamivir clinical study reports, and appendices were found in ~~M~~modules 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~~Risk of bias assessments were ~~therefore therefore~~ based on each ~~clinical study report's c~~core report. Subsequently

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7 119 in 2013, we obtained full clinical study reports from Roche, and as part of a further  
8 120 systematic review update, carried out new risk of bias assessments of the same trials  
9 121 based on the full clinical study reports.  
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11 122 ~~We Our overall aim was aimed~~ to investigate whether ~~and how~~ the level of detail ~~contained~~  
12 123 in reports ~~ofing a trials~~ affects judgments about risk of bias. ~~We planned to achieve this,~~  
13 124 ~~by comparing documents which containing increasingly detailed reports~~ information on  
14 125 each trial included in our review, namely journal publications, core reports, and full clinical  
15 126 study reports. ~~for each trial included in our reviews by comparing reports of the same trial~~  
16 127 ~~with widely varying level of detail. These were journal publications, core reports, and full~~  
17 128 ~~clinical study reports.~~ As well as using the standard Cochrane risk of bias tool, we  
18 129 developed an additional list of study elements we wanted to extract ~~in order to allow~~  
19 130 ~~improved assessments of to help us better judge ee~~ each trial's design and conduct and  
20 131 ~~help us in the task of~~ facilitate the organization of organizing large quantities of information  
21 132 now available to us.

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22 133 In this report we describe our use of these tools to address three specific questions:  
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24 134  
25 135 1. Do core reports change the risk of bias evaluation compared to published papers?  
26 136 2. Do full clinical study reports change the risk of bias evaluation compared to core  
27 137 reports?  
28 138 3. Do full clinical study reports change the risk of bias evaluation compared to  
29 139 published papers?  
30 140

31 141 ~~In summary we intended to analyze whether progressively greater amounts of information~~  
32 142 ~~and detail in clinical study reports (including trial protocols, statistical analysis plans,~~  
33 143 ~~certificate of analyses, individual participant data listings and randomization lists) affected~~  
34 144 ~~our risk of bias assessments~~

35 145 **Methods**

36 146 ~~Ten C~~core reports ~~for 14 trials contained in 10 Clinical study reports~~ (M76001; ~~NV16871~~;  
37 147 WV15670; WV15671; WV15707; WV15730; WV15759/WV15871; WV15799;  
38 148 WV15812/WV15872; WV15819/WV15876/WV15978; ~~NV16874~~) were received ~~in pdf~~PDF  
39 149 files from Roche and EMA by 12 April 2011 (the date of time-lock for our ~~2012~~ Cochrane  
40 150 review).[6] ~~The reporting of more than one trial in the same clinical study report was~~  
41 151 ~~justified by Roche as a consequence of lower than expected participant recruitment due to~~  
42 152 ~~low influenza circulation and consequently a need to pool studies.~~

43 153 The current Cochrane risk of bias tool ~~was first introduced in 2010. The tool~~ consists of six  
44 154 domains, each may have more than one source of bias application, depending on the  
45 155 subject matter.[7] Our applications were as follows: selection bias (random sequence  
46 156 generation and allocation concealment), performance bias (blinding of participants and  
47 157 personnel – all outcomes), detection bias (blinding of outcome assessment - all  
48 158 outcomes), attrition bias (influenza symptoms, complications and harms outcome data),  
49 159 reporting bias (selective reporting) and other bias. The identification of sources- of other  
50 160 bias was left at the reviewers' discretion.

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

~~R~~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.~~

After 12<sup>th</sup> 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 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](http://www.bmj.com/tamiflu/roche)). ~~Fifteen clinical study reports containing Twenty~~20 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 ~~c~~clinical 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, the redactions did not impede ~~an our~~ analyses 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 ~~however which~~ 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 product~~ were 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; NV16871; WV15730; 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 (including notably, in the Kaiser et al pooled analysis of ten trials, eight of which were unpublished[13]) and not 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 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 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-full](#) clinical study reports, Table [4-2](#) 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 [42](#)).

[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 “compli harms” 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 [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 reports~~ing~~. ~~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" 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 dataset directly. However even with individual participant data, some forms of bias, such as attrition bias, may still be difficult to quantify. In such a situation it is impossible to quantify bias because withdrawals are lost, it seems to make little sense to quantify, 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, afford provides an opportunity to think about consider both actual as well as a risk of biases.

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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 simply 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 level 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 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 question 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 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

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](http://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 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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**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 ITT intention-to-treat population was described and reported in a table. However when the full CSR clinical study report became available we realised that the original protocol was missing.



<u>Trial(s)</u>	<u>Risk of bias assessment performed based on</u>			
<u>Trial(s)</u>	<u>Pooled analysis</u> [13] (2009 Cochrane review [22])	<u>Journal publication</u> (2007, 2009 and 2010 Cochrane reviews [12,22,23])	<u>Core report</u> (2012 Cochrane review [6])	<u>Full clinical study report</u> (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	X		X	X
WV15978				

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 24. 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 32. 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			Total, n (%)
	High, n (%)	Unclear, n (%)	Low, 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 of oseltamivir trials with and without allowing unclear assessments in sensitivity analysis.

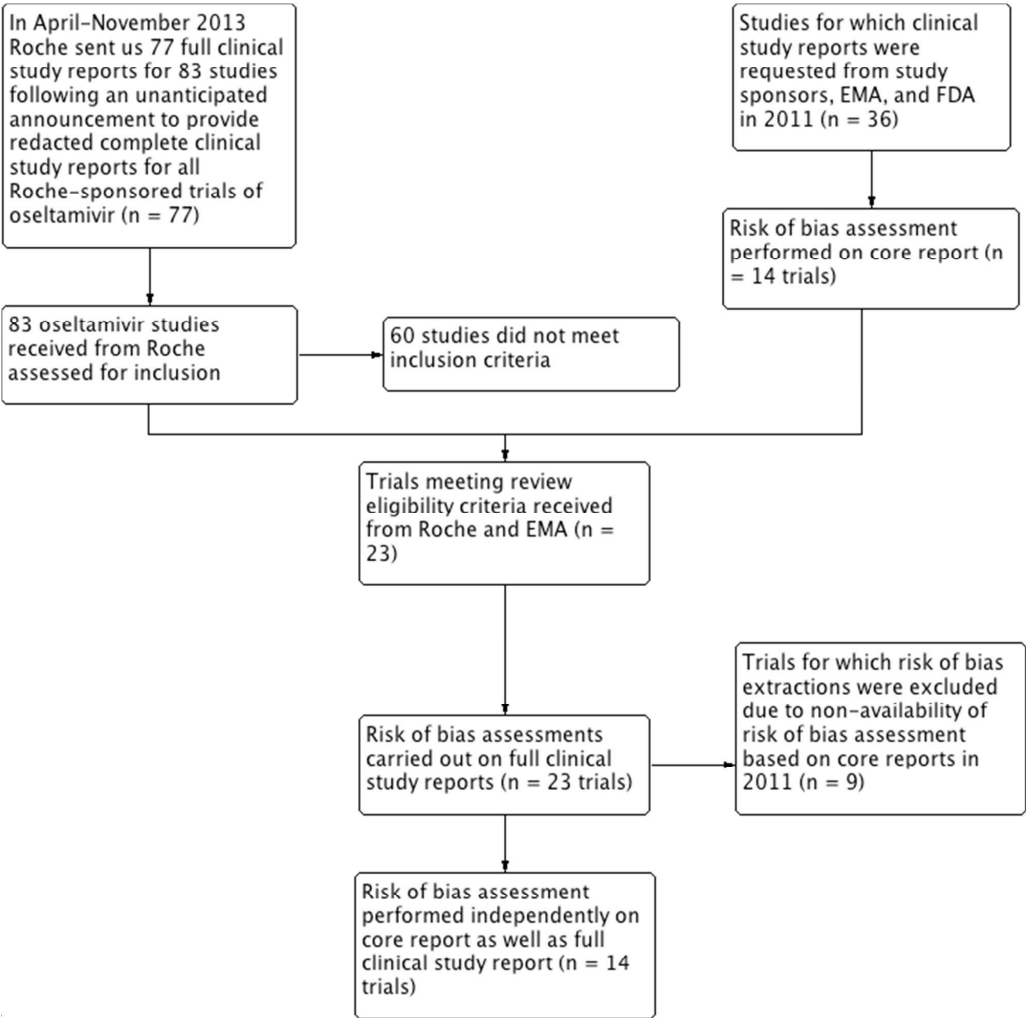


Figure 1. Study flow diagram

For peer review only

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

16

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



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

### 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	<b>METHODS</b>			
1a	○ Study Design	RPS		
1b	○ Location, number of centers	RPS LIESA		
1c	○ Duration of study	RPS		
2	<b>PARTICIPANTS</b>			
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	<b>INTERVENTIONS</b>			

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 (performance 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

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**FUC** = Follow up cards/Diary cards

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**RAP** = Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan (SAP))

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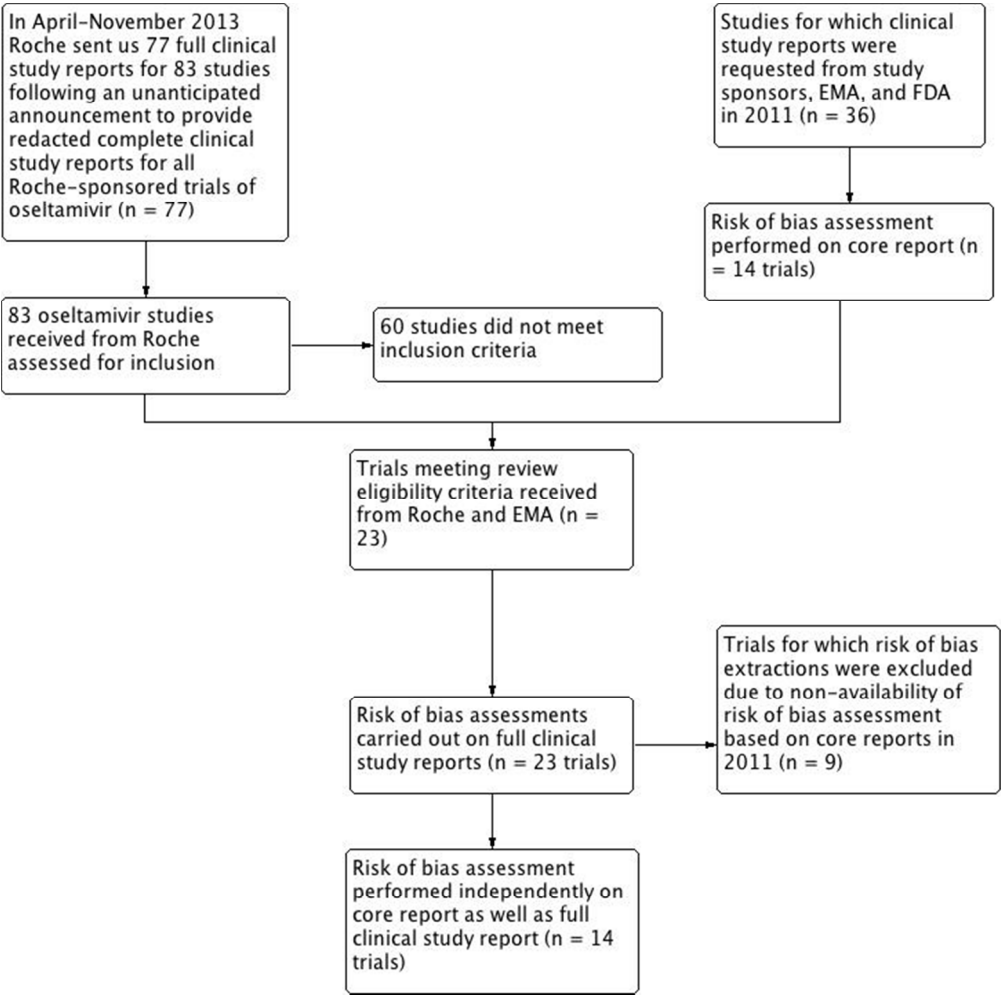


Figure 1 Flow Chart  
256x253mm (72 x 72 DPI)

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16

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5.3.5.4.6 CSR WV15799 (W-144170)

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4a	○ Primary outcome	RPS RAP CRF  Note: ensure CRF can capture relevant info		
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5	<b>NOTES</b>			Make any other points you wish here
6	<b>RISK OF BIAS</b>			
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	<ul style="list-style-type: none"><li>○ Selective reporting (reporting bias)</li></ul>	RPS IC LIESA  Note: check if all contributors listed in core report are present in protocol and LIESA		
6e	<ul style="list-style-type: none"><li>○ Other bias</li></ul>	RPS		
6f	<ul style="list-style-type: none"><li>○ Blinding of participants and personnel (performance bias)</li></ul>	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	<ul style="list-style-type: none"><li>○ Blinding of outcome assessment (detection bias)</li></ul>	RPS CA  Note: ensure CA supports description of placebo and active elsewhere in CSR		

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# BMJ Open

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

Journal:	BMJ Open
Manuscript ID:	bmjopen-2014-005253.R2
Article Type:	Research
Date Submitted by the Author:	03-Sep-2014
Complete List of Authors:	Jefferson, Tom; The Cochrane Collaboration, Cochrane ARI Group Jones, Mark; University of Queensland, School of Population Health Doshi, Peter; University of Maryland, School of Pharmacy Del Mar, Chris; Bond University, Faculty of Health Sciences and Medicine Hama, Rokuro; Japan Institute of Pharmacovigilance, Director Thompson, Matthew; University of Oxford, Department of Primary Care Health Sciences Onakpoya, Igho; University of Oxford, Primary Care Health Sciences Heneghan, Carl; Oxford University, Primary Health Care
<b>Primary Subject Heading</b>:	Evidence based practice
Secondary Subject Heading:	Research methods, Qualitative research
Keywords:	STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

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4 Thompson<sup>6,7</sup>, Igbo Onakpoya<sup>7</sup>, Carl J Heneghan<sup>7</sup>

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## 21 Abstract

22 Words: 280

## 23 Background

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

## 31 Methods and Findings

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

## 43 Conclusions

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

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54 Strengths and limitations of this study

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- 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

## 70 Introduction

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

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

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

88 Although there is some variation in the structure and content of clinical study reports, they  
89 are usually composed of a core report of the trial and appendices. A core report (sections  
90 1-15 of the ICH E3 document) is structured in Introduction, Methods Results And  
91 Discussion (IMRAD) style. The numerous appendices (section 16 of ICH E3) contain  
92 important supplementary data needed to understand and interpret the trial, its context and  
93 history.[1,2] These appendices include such documents as the trial protocol, protocol  
94 amendments, statistical analysis plan, blank case report forms, certificates of analysis,  
95 randomization lists, and consent forms. For the purposes of this paper the core report plus  
96 all its appendices will be known as the full clinical study report. (See Appendix 1 for the  
97 table of contents of a typical oseltamivir clinical study report and  
98 <http://dx.doi.org/10.5061/dryad.77471> for free download of all the clinical study reports  
99 used in our review and featured in this paper. The core report was known as Module 1 in  
100 oseltamivir clinical study reports, and appendices were found in Modules 2-5.) Core  
101 reports and full clinical study reports theoretically can help reduce uncertainty in judging  
102 risk of bias.

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

109 Our overall aim was to investigate whether the level of detail contained in reports of trials  
110 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 12<sup>th</sup> 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](http://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

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

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

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

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

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

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

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

## 194 Results



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3 195 We could only compare risk of bias assessments between core reports and full clinical  
4 196 study reports for the following 14 trials (reported in 10 clinical study reports): M76001;  
5 197 NV16871; WV15670; WV1Z5671; WV15707; WV15730; WV15759/WV15871; WV15799;  
6 198 WV15812/WV15872; WV15819/WV15876/WV15978 (Figure 1 and Table 1).

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9 199 We could not carry out a comparison of risk of bias judgments of journal publications with  
10 200 core reports or full clinical study reports, because our assessments were largely based on  
11 201 secondary publications (notably, the Kaiser et al pooled analysis of ten trials, eight of  
12 202 which were unpublished[13]) rather than primary publications of the trials, and also utilized  
13 203 an outdated risk of bias tool. There were therefore too few studies (3) for which we had  
14 204 distinct risk of bias judgments of primary journal publications (many studies for which we  
15 205 have clinical study reports were and remain unpublished, for example 8 of the 13 trials in  
16 206 adults). In addition, the current Cochrane risk of bias tool was introduced after the  
17 207 production of our review of published articles, making the comparison, had we had the  
18 208 data to undertake it, more difficult to interpret and possibly unfair.

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22 209 For the comparison of core and full clinical study reports, Table 2 shows that no previous  
23 210 assessment of “high” risk of bias was reclassified as “low” or “unclear” in the presence of  
24 211 more detailed information. Previous assessments of “low” risk of bias were not  
25 212 uncommonly reclassified as “high” bias in the subsequent assessment. While our  
26 213 assessments based on core reports were mostly classified as “low risk of bias” they were  
27 214 reclassified in the opposite direction as “high” risk of bias when our judgments were based  
28 215 on full clinical study reports (Table 2).

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30 216 A spreadsheet recording all individual risk of bias judgments is available on line, see  
31 217 supplemental file 1.

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35 218 Had we kept the “unclear” risk of bias judgment option when assessing full clinical study  
36 219 reports [10] we would have had 64 “unclear” judgments (see sensitivity analysis in Table  
37 220 3). The breakdown of these 64 into the various attributes is:

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40 221 • Attrition bias: symptoms (10); complications (9); safety (15). These were unclear  
41 222 because we do not know the impact of missing symptoms data, the reports  
42 223 contained unclear definitions for secondary complications of influenza, and a  
43 224 seemingly problematic decision tool for the alternative designation of events as  
44 225 either complications or harms, which we called “compliharms” in our Cochrane  
45 226 review.

46  
47 227 • Other bias (13) – these are unclear due to the unknown effect of the dehydrocholic  
48 228 acid included in the placebo but not included in the active treatment

49  
50 229 • Performance bias (6) – these are unclear due to missing certificates of analysis  
51 230 describing the placebo appearance

52  
53 231 • Selection bias (10) – these are unclear due to the missing or unclear randomisation  
54 232 lists meaning we cannot confirm random sequence generation

55  
56 233 • Detection bias (1) – unclear due to unknown impact of different coloured placebo  
57 234 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

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3 276 example, the original trial protocol is available, one can judge whether reporting bias  
4 277 occurred. Reviewers need not guess at bias (i.e. make a judgment of “risk”) but can judge  
5 278 bias directly. However even with individual participant data, some forms of bias, such as  
6  
7 279 attrition bias, may still be difficult to quantify, and one can only judge the risk (i.e. potential)  
8 280 of bias. Therefore access to detailed information and participant level data sometimes  
9 281 found in full clinical study reports, provides an opportunity to consider both *actual* as well  
10 282 as *risk of biases*.

11  
12 283 Box 1 shows examples of the types of information found in clinical study reports that led to  
13 284 risk of bias assessment changes. While the judgments of “low” or “high” risk of bias may  
14 285 imply certainty, particularly when based on the reading of a full clinical study report, we  
15 286 found ourselves often in lengthy debate and discussion over the proper level of risk of bias  
16 287 before arriving at a consensus. We found the risk of bias judgments themselves to carry a  
17 288 high level of subjectivity, in which different judgments can be justified in different ways.  
18 289 The real strength of the risk of bias tool appears not to be in the final judgments it enables,  
19 290 but rather in the process it helps facilitate: critical assessment of a clinical trial.

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23 291 Another aspect to emerge is that tools based on publications are designed to detect  
24 292 presence, absence or uncertainty regarding elements in a very restricted number of places  
25 293 in the text. The availability of full clinical study reports allows reviewers to follow  
26 294 consistency across chapters and appendices, creating a need for far more interaction with  
27 295 the text. An example of this active engagement is the cross-checking of active principle  
28 296 and placebo batches used across trials and their connection with a visual description of  
29 297 their properties such as color in a certificate of analysis. For example, once the presence  
30 298 of a differently colored placebo capsule cap in trial WP16263 was identified through the  
31 299 clinical study report’s certificate of analysis, its potential impact on blinding was captured in  
32 300 the Cochrane instrument. The interpretation of such a finding is difficult, as the colors of  
33 301 the active principle and placebo capsule caps are close (ivory and light yellow). However  
34 302 publication-based or core report only based assessments would not have identified the  
35 303 potential differences in color as the descriptions are simply given as “placebo” [14] and  
36 304 “matching placebo” [15] respectively. Reviewing complete clinical study reports and our  
37 305 assessment of bias was very time consuming, necessitating prolonged exchanges  
38 306 including a face-to face meeting given the novelty of what we were doing. This activity  
39 307 though was not as difficult or as time consuming as the reconstruction of trial evidence  
40 308 programmes for oseltamivir, an activity which necessitated a whole time equivalent  
41 309 researcher for 6 months. However because of the threat of reporting bias we can think of  
42 310 no alternative to the use of full clinical study reports.

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45 311 The main limitation of our study is our relative inexperience in dealing with large quantities  
46 312 of information and our lack of familiarity with certain trial documents such as randomization  
47 313 lists. Randomization lists appeared to be of two types. The first was a pre-randomization  
48 314 list of random codes with which participants’ IDs cannot be matched with the participant  
49 315 IDs used within other sections of the clinical study report. The second was a post-hoc  
50 316 randomization list to which individual participants can be matched but the original  
51 317 generated codes are not shown. In both cases the truly random generation of the  
52 318 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.

**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 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**

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2  
3 357 Dr Jefferson receives royalties from his books published by Blackwells and Il Pensiero  
4 358 Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research  
5 359 companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In  
6 360 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to an  
7 361 antiviral (oseltamivir phosphate; Tamiflu [Roche]) and in a labour case on influenza  
8 362 vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as consultant  
9 363 for Roche, in 2001-2 for GSK and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-  
10 364 rhinoviral which did not get approval from FDA). Dr Jefferson was a consultant for IMS  
11 365 Health in 2013 and is currently retained as a scientific advisor to a legal team acting on the  
12 366 drug Tamiflu (oseltamivir, Roche). Dr Jefferson recently had part of his expenses  
13 367 reimbursed for attending the annual (UK) Pharmaceutical Statisticians' Conference.  
14  
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17 368 Dr Doshi received €1500 from the European Respiratory Society in support of his travel to  
18 369 the society's September 2012 annual congress in Vienna, where he gave an invited talk on  
19 370 oseltamivir. Dr Doshi is an associate editor at The BMJ.  
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21  
22 371 Dr Del Mar was a Board member of two companies to commercialise research at Bond  
23 372 University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010 and  
24 373 receives fees for editorial and guideline developmental work and royalties from books and  
25 374 in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a  
26 375 private donor (for support of the editorial base of the Cochrane ARI Group).  
27  
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29 376 Dr Hama receives royalties from two books published in 2008 titled "Tamiflu: harmful as  
30 377 was afraid" and "In order to escape from drug-induced encephalopathy". Dr Hama  
31 378 provided scientific opinions and expert testimony on 11 adverse reaction cases related to  
32 379 oseltamivir and gefitinib.  
33  
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35 380 Drs Onakpoya, Thompson, Jones and Heneghan have no additional interests to disclose.  
36  
37 381 **Data Sharing.** The source core reports and clinical study reports can be found at  
38 382 <<http://datadryad.org/resource/doi:10.5061/dryad.77471>>. A spreadsheet recording all  
39 383 individual risk of bias judgments is available in an online supplemental file to this paper.  
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**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.

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7 1 **Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus**  
8 2 **full clinical study reports**  
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10 3 Tom Jefferson<sup>1</sup>, Mark A Jones<sup>2</sup>, Peter Doshi<sup>3</sup>, Chris B Del Mar<sup>4</sup>, Rokuro Hama<sup>5</sup>, Matthew J  
11 4 Thompson<sup>6,7</sup>, Igbo Onakpoya<sup>7</sup>, Carl J Heneghan<sup>7</sup>  
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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 reported-assessed in other Cochrane review s assessments limited to based on published research journal publications.

## Strengths and limitations of this study

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- 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

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7 112 which contain increasingly detailed information on each trial included in our review, namely  
8 113 journal publications, core reports, and full clinical study reports. As well as using the  
9 114 standard Cochrane risk of bias tool, we developed an additional list of study elements we  
10 115 wanted to extract in order to allow improved assessments of each trial's design and  
11 116 conduct and facilitate the organization of large quantities of information now available to  
12 117 us.  
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14 118 In this report we describe our use of these tools to address three specific questions:  
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- 16 119 1. Do core reports change the risk of bias evaluation compared to published papers?  
17 120 2. Do full clinical study reports change the risk of bias evaluation compared to core  
18 121 reports?  
19 122 3. Do full clinical study reports change the risk of bias evaluation compared to  
20 123 published papers?  
21

22 124 **Methods**  
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24 125 Ten core reports (M76001; NV16871; WV15670; WV15671; WV15707; WV15730;  
25 126 WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978)  
26 127 were received in PDF files from Roche and EMA by 12 April 2011 (the date of time-lock for  
27 128 our 2012 Cochrane review).[6] The reporting of more than one trial in the same clinical  
28 129 study report was justified by Roche as a consequence of lower than expected participant  
29 130 recruitment due to low influenza circulation and consequently a need to pool studies.  
30 131

31 132 The current Cochrane risk of bias tool consists of six domains, each may have more than  
32 133 one source of bias application, depending on the subject matter.[7] Our applications were  
33 134 as follows: selection bias (random sequence generation and allocation concealment),  
34 135 performance bias (blinding of participants and personnel – all outcomes), detection bias  
35 136 (blinding of outcome assessment - all outcomes), attrition bias (influenza symptoms,  
36 137 complications and harms outcome data), reporting bias (selective reporting) and other  
37 138 bias. The identification of sources of other bias was left at the reviewers' discretion.  
38 139

39 140 Risk of bias assessments were performed following Cochrane methods [7] and published  
40 141 in 2012.[6] In that review, risk of bias was assessed by an external reviewer on the basis  
41 142 of data extracted from core reports.  
42

43 143 After 12<sup>th</sup> April 2011, we obtained the appendices of the clinical study reports included in  
44 144 our review. For most clinical study reports we requested, EMA had the protocol, protocol  
45 145 amendments, statistical analysis plan, blank case report forms, and other appendices  
46 146 contained in what Roche terms the second "module" of a full clinical study report (see  
47 147 Appendix 1). However EMA did not possess—and therefore could not provide us with—full  
48 148 clinical study reports with the exception of trial WP16263.[8] For approximately three years  
49 149 Roche had repeatedly refused our requests for full clinical study reports.[9]  
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51 150 In April 2013 in the course of carrying out these new extractions, Roche changed its policy  
52 151 on access to data and pledged to share with us 77 full clinical study reports  
53 152 (www.bmj.com/tamiflu/roche). Fifteen clinical study reports containing 20 trials were  
54 153 included in the analysis of our current review.[10] As we were already in possession of  
55 154 core reports and appendices such as the protocol and statistical analysis plan for the 14  
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7 155 trials in this analysis, the additional data for other clinical study reports provided by Roche  
8 156 does not concern this paper. In the clinical study reports Roche redacted information that  
9 157 they judged to be of "legitimate commercial interest" or present a risk of trial participant re-  
10 158 identification. The redactions did not impede our analyses of risk of bias.

11  
12 159 Based on our growing familiarity with clinical study reports, we designed and piloted a  
13 160 data extraction sheet to record how our understanding of the trials changed in light of  
14 161 availability of the additional appendices. We realized that in addition to the standard  
15 162 Cochrane risk of bias elements, we needed to organize the abundant material at our  
16 163 disposal and re-construct a timeline of the trials. We used the Cochrane risk of bias tool [7]  
17 164 to appraise clinical study reports and a data extraction sheet for recording information  
18 165 relevant to this appraisal. We added the following elements to our extraction sheets: date  
19 166 of participant enrollment, unblinding of the trial, protocol for which we had the full text,  
20 167 protocol amendments, statistical analysis plan for which we have the full text (and its  
21 168 amendments), patient consent form, randomization list, and certificate of analysis.  
22 169 Timeline reconstruction allowed us to conceptualise the design and conduct of the trials  
23 170 and appreciate their role in the trial programme with their strengths and limitations. In  
24 171 addition following a timeline allows a judgment to be made on the integrity and temporal  
25 172 sequence of the documents. The finalized extraction sheet is in Appendix 2.

26 173 Based on access to full clinical study reports, we carried out our final assessment of risk of  
27 174 bias. These were carried out by a single reviewer, checked by a second with final  
28 175 consensus reached through a face-to-face discussion among the entire group.

29 176 Because with full clinical study reports there should be no ambiguity, we only allowed "low"  
30 177 or "high" risk of bias judgments (i.e. no "unclear"). We adopted the position that, unlike a  
31 178 publication which may have page limits, there was no reason a full clinical study report  
32 179 should be missing details necessary for a third party to judge risk of bias. Therefore, when  
33 180 information that would have otherwise allowed us to judge a risk of bias as either "low" or  
34 181 "high" was missing, this would automatically be categorized as "high" risk of bias. This  
35 182 decision to eliminate the "unclear" option when assessing full clinical study reports was  
36 183 made following an initial assessment of the trials, which included "unclear" judgments.  
37 184 Based on earlier peer-review of this paper which suggested we analyze the data had we  
38 185 kept the "unclear" category, we also carried out this post-hoc analysis.

39 186 To allow for a comparison of risk of bias judgments based on published reports of trials  
40 187 and risk of bias judgments based on clinical study reports (either core reports alone or full  
41 188 clinical study reports), we used our previous risk of bias judgments for the same trials in  
42 189 the relevant Cochrane reviews that had been based on publications.[11,12]

43 190 The extraction and adjudication methods used were the same as those used in our  
44 191 subsequent unified Cochrane review.[6] We used descriptive methods to answer our three  
45 192 questions without the need for formal statistical analysis.

46 193 Ethics approval and patient consent were not necessary for this study.

## 47 194 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 supplementary 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 “compli harms” 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, 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.

**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 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.



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**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.

Trial(s)	Risk of bias assessment performed based on			
	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	x		x	x
WV15978				

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
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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.

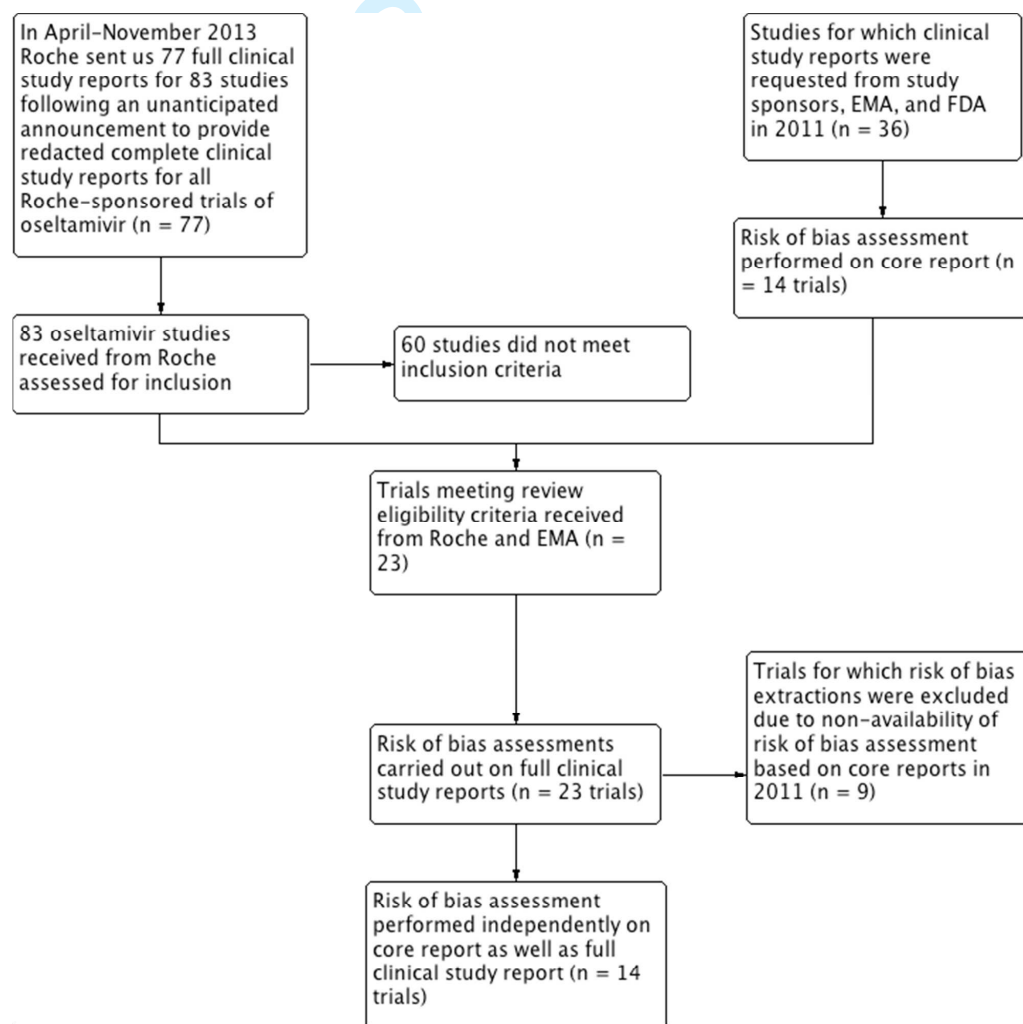


Figure 1. Study flow diagram

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

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Tamiflu® (oseltamivir phosphate)

75mg Capsules, Hard

12 mg/mL Oral Suspension



5.3.5.4.6 CSR WV15799 (W-144170)

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CLINICAL STUDY REPORT MODULES

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This report consists of 5 modules.

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

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

### 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	o Study Design	RPS		
1b	o Location, number of centers	RPS LIESA		
1c	o Duration of study	RPS		
2	PARTICIPANTS			
2a	o Number screened	-	LEAVE BLANK UNLESS NEEDED	LEAVE BLANK UNLESS NEEDED
2b	o Number randomized	-		
2c	o Number completed	-		
2d	o Number analysed	-		
2e	o Male/Female ratio	-		
2f	o Mean age	-		
2g	o Baseline details	-		
2h	o Inclusion criteria	RPS		
2i	o Exclusion criteria	RPS		
2j	o 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 (performance 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.

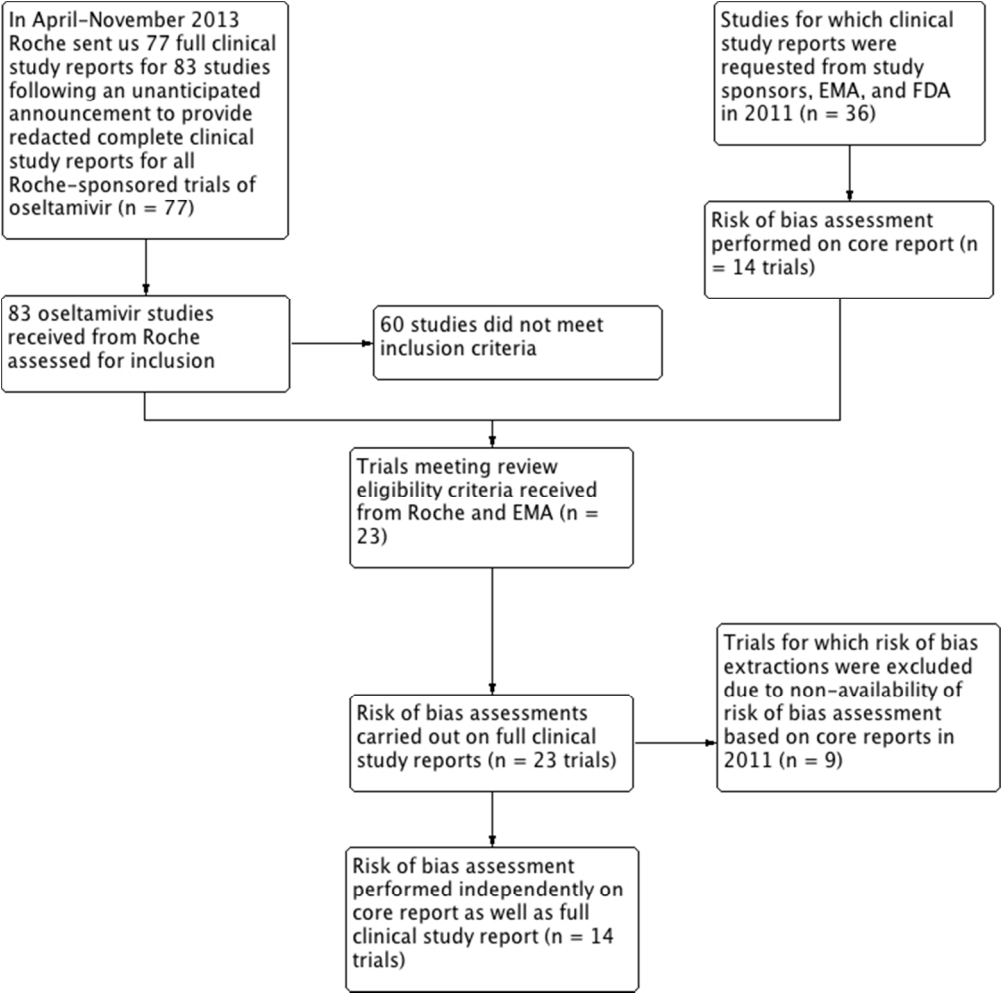


Figure 1 Flow chart  
256x253mm (72 x 72 DPI)



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

16

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



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.

<b>MODULE I:</b>	<b>CORE REPORT</b>
	Background and Rationale
	Objectives
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	Statistical Analysis
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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

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CSR for trial(s):	
Reviewer:	
Date(s) of extraction:	

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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

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G	Patient consent form			
H	Randomization list			
I	Certificate of Analysis			

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1c	○ Duration of study	RPS		
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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		
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3	INTERVENTIONS			

3a	○ Intervention	RPS CA RAP		
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3f	○ Co-interventions	RPS RAP		
4	OUTCOMES			
4a	○ Primary outcome	RPS RAP CRF  Note: ensure CRF can capture relevant info		
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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 (performance 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
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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
M76001	A159: Incomplete outcome data (attrition bias) safety	Low	
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
M76001	A159: Blinding of outcome assessment (detection bias)		
M76001	All outcomes	Low	
M76001	Random sequence generation (selection bias)	Low	
NV16871	Allocation concealment (selection bias)	Low	

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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 generating random numbers not clear
WV15670	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating random numbers not clear "The randomisation numbers were generated by a computer program (Random Sequence Generator, Inc., Princeton, NJ, USA)."
WV15670	Allocation concealment (selection bias)	Low	"The investigator telephoned the centre to report the randomization number was then supplied by a computer system (IVRS). The investigator entered the randomization number into the system."
WV15670	Incomplete outcome data (attrition bias), symptoms	High	Available data analyzed by ITTI population and not by ITTI population
WV15670	Incomplete outcome data (attrition bias), complications in the infected subpopulation non-responders	High	Possible effect of oseltamivir on antibody production and neutralization

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WV1567 0	complications of influenza Incomplete outcome data (attrition bias), safety data	Low	Based on all participants irrespective of compliance
WV1567 0	Selective reporting (reporting bias), other bias	High	Outcomes of primary interest for the ITT population
WV1567 0	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage not "In order to maintain blinding, each subject had 2 capsules administered from each bottle twice per day at the first (day 1) visit Each bottle was labelled with the subject number and the word placebo. Those subjects receiving 75 mg bid received a matching capsule containing placebo from the bottle. Those received one capsule containing 75 mg active drug from the bottle. "No open key to the randomisation code was available at Roche Headquarters. In the event of a medical emergency necessary to properly manage the subject, by consent of the The blinding was not required to be broken for any reason Described as randomised; procedure generating
WV1567 0	Blinding of participants and personnel (performance bias), all outcomes	Low	
WV1567 0	Blinding of outcome assessment (detection bias), all outcomes	Low	
WV1567 0	Random sequence	Unclear	

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1					
2					
3					
4	1	generation (selection		randomisations schedule not available	
5		bias)			
6					
7				“Randomisation was conducted by a central rand	
8				The investigator /study coordinator telephoned th	
9				the subjects initials, date of birth and smoking his	
10				randomisations	
11	WV1567	Allocation concealment		number was entered in the appropriate	
12	1	(selection bias)	Low	place on the subject’s Case Report Form by th	
13		Incomplete outcome			
14	WV1567	data (attrition bias),		Data from study participants without influen	
15	1	symptoms	Low	were available for symptom relief	
16				Possible effect of oseltamivir on antibody	
17		Incomplete outcome		production makes the assessment of influenza	
18		data (attrition bias),		status and associated complications	
19	WV1567	complications of		in the infected subpopulation non-comparable	
20	1	influenza	High	between the treatment groups	
21		Incomplete outcome			
22	WV1567	data (attrition bias),		Based on all participants irrespective of	
23	1	safety data	Low	compliance with treatment or infection status	
24		Selective reporting			
25	WV1567	(reporting bias), other		Outcomes of primary interest for the ITT	
26	1	bias	Low	population available in the CONSORT reconstr	
27	WV1567				
28	1	Other bias	High	Placebo contained dehydrocholic acid	
29				Matching placebo used	
30				“In order to maintain the double blind nature	
31				of the study, subjects received 2 capsules	
32				twice daily for all treatments.”	
33		Blinding of participants		“The identification number was added by	
34		and personnel		the investigator at the time of randomisations	
35		(performance bias), all		“No open key to the code was available at	
36	WV1567	outcomes	Low	the Study Center...”	
37	1			“The identification number was added by	
38				the investigator at the time of randomisations	
39		Blinding of outcome		“No open key to the code was available at	
40	WV1567	assessment (detection		the Study Center, to the Monitors, Statistician	
41	1	bias), all outcomes	Low	or at Gilead/Roche Headquarters”	
42	WV1567				
43	3	Random sequence			
44	WV1569	generation (selection			
45	7	bias)	Unclear	Described as randomised; procedure generating r	
46	WV1567				
47	3	Allocation concealment			
48	WV1569	(selection bias)	Unclear	Inadequate information available to ascertain cor	
49					
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7				
WV1567				
3	Incomplete outcome			
WV1569	data (attrition bias),			
7	symptoms	Low		Not applicable to the study design (prophylaxis)
WV1567	Incomplete outcome			
3	data (attrition bias),			
WV1569	complications of			Possible effect of oseltamivir on antibody product
7	influenza	High		complications in the infected subpopulation non-
WV1567	A159: Incomplete			
3	outcome data (attrition			
WV1569	bias)			
7	Safety data	Low		Based on all randomised participants
WV1567				
3	A159: Selective			
WV1569	reporting (reporting			
7	bias)	Low		Outcomes of primary interest for the ITT population
WV1567				
3				
WV1569				
7	A159: Other bias	Unclear		Placebo contained dehydrocholic acid. Dosage
WV1567	A159: Blinding of			
3	participants and			
WV1569	personnel (performance			
7	bias)	Unclear		Capsule size, but no details of colour or taste
WV1567	All outcomes			
3	A159: Blinding of			
WV1569	outcome assessment			
7	(detection bias)	Unclear		Inadequate information available to ascertain wh
WV1570	All outcomes			
7	Random sequence			
WV1570	generation (selection			
7	bias)	Unclear		Described as randomised; procedure generating r
WV1570	Allocation concealment			"Randomization was performed by a central rand
7	(selection bias)	Low		the subject's date of birth, vaccination status and
WV1570	Incomplete outcome			
7	data (attrition bias),			
WV1570	symptoms	High		Available data analyzed by ITTI population and no
WV1570	Incomplete outcome			
7	data (attrition bias),			
WV1570	complications of			Possible effect of oseltamivir on antibody product
7	influenza	High		complications in the infected subpopulation non-

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WV1570	7	A159: Incomplete outcome data (attrition bias)	Low	Based on all randomised participants
WV1570	7	Safety data	High	Outcomes of primary interest for the ITT population
WV1570	7	A159: Selective reporting (reporting bias)	Unclear	Placebo contained dehydrocholic acid. Dosage not stated
WV1570	7	A159: Other bias	Low	Presentation of placebo described as identical
WV1570	7	A159: Blinding of participants and personnel (performance bias)	Unclear	Inadequate information available to ascertain whether participants were blinded
WV1570	7	All outcomes	Unclear	Randomization numbers generated by Roche, not independent
WV1570	8	A159: Blinding of outcome assessment (detection bias)	Unclear	Insufficient details given
WV1570	8	Allocation concealment (selection bias)	Low	Outcomes available on all patients who completed the study
WV1570	8	Incomplete outcome data (attrition bias), symptoms	Low	Outcome data on all patients provided.
WV1570	8	Incomplete outcome data (attrition bias), complications of influenza	Low	Outcome data reported.
WV1570	8	A159: Incomplete outcome data (attrition bias)	Unclear	Placebo contents and colour and similarity to active treatment not stated
WV1570	8	Safety data	Low	could not analyze for primary outcome of efficacy
WV1570	8	A159: Selective reporting (reporting bias)	Low	
WV1570	8	A159: Other bias	Low	
WV1570	8	A159: Blinding of participants and personnel (performance bias)	Low	
WV1570	8	All outcomes	Low	

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WV1570	8	A159: Blinding of outcome assessment (detection bias) All outcomes Random sequence generation (selection bias)	Low	Outcome assessors were blind
WV1573	0	Allocation concealment (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available "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 randomisations service."
WV1573	0	Incomplete outcome data (attrition bias), symptoms	High	Available data analysed by ITTI population and not ITT 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
WV1573	0	Incomplete outcome data (attrition bias), complications of influenza	High	
WV1573	0	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
WV1573	0	Selective reporting (reporting bias), other bias	High High	Outcomes of primary interest for the ITT population not made available to the review
WV1573	0	Other bias		Placebo capsule contained dehydrocholic acid
WV1573	0	Blinding of participants and personnel (performance bias), all outcomes	Low	Matching placebo. "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"
WV1573	0	Blinding of outcome assessment (detection bias), all outcomes	Low	
WV1575	8	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV1575	8	Allocation concealment (selection bias)	Low	"Randomization was conducted by a central randomisations service, ICTI (Interactive

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				Clinical Technologies Inc., Princeton, NJ). The investigator telephoned the centre to report the subject’s date of birth, sex, and 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.”
WV1575	8	Incomplete outcome data (attrition bias), symptoms	Low	Data available for both influenza infected and non-infected study populations
WV1575	8	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
WV1575	8	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomized patients
WV1575	8	Selective reporting (reporting bias), other bias	Low	Outcomes of primary interest to the review for ITT population available in the CONSORT-based extraction reconstruction
WV1575	8	Other bias	Unclear	Unable to ascertain placebo capsule contents
WV1575	8	Blinding of participants and personnel (performance bias), all outcomes	Low	“No open key to the code was available at the study centre...”
WV1575	8	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.”
WV1587	1	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV1575	9			The subject randomizations numbers will be generated by Roche or its designee and incorporated
WV1587	1	Allocation concealment (selection bias)	Low	Randomization will be conducted by a central randomization service by telephone.
WV1587	1	Incomplete outcome data (attrition bias), symptoms	Unclear	Insufficient information was available to ascertain populations for analysis and judge risk of bias

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WV1575	Incomplete outcome data (attrition bias),		Insufficient information was available to ascertain
9	complications of		populations for analysis and judge
WV1587	influenza	Unclear	risk of bias
1			
WV1575	Incomplete outcome data (attrition bias),		Insufficient information was available to ascertain
9	safety data	Unclear	populations for analysis and judge
WV1587			risk of bias
1	Selective reporting (reporting bias), other bias	High	No outcome data were provided in the study CONSORT-based extraction reconstruction
WV1575			
9			
WV1587	Other bias	High	Placebo capsule contained dehydrocholic acid
1	Blinding of participants and personnel		
WV1575	(performance bias), all outcomes	Low	Matching placebo
9			
WV1587	Blinding of outcome assessment (detection bias), all outcomes	Unclear	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment
1	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating randomisations schedule not available
WV1579	Allocation concealment (selection bias)	Unclear	Inadequate information available to ascertain concealment of allocation
9	Incomplete outcome data (attrition bias), symptoms	Low	Not applicable to the study design (prophylaxis)
9	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
WV1579	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants
9	Selective reporting (reporting bias), other bias	High	Outcome data for ITT population were not available to the review authors

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WV1579				
9	Other bias	Unclear	No information available on placebo contents	
	Blinding of participants and personnel			
WV1579	(performance bias), all		Inadequate information available to ascertain	
9	outcomes	Unclear	presentation of placebo capsules	
	Blinding of outcome		Inadequate information available to ascertain	
WV1579	assessment (detection		whether outcome assessors were aware	
9	bias), all outcomes	Unclear	of treatment group assignment	
WV1581				
2	Random sequence			
WV1587	generation (selection			
2	bias)	Unclear	Described as randomised; procedure generating random numbers	
WV1581			"The randomisation numbers were generated by RAND Inc., Princeton, NJ, USA)."	
2			"The investigator telephoned the centre to report the randomization number was then supplied by the system (IVRS). The investigator entered the randomization number into the system (IVRS)."	
WV1587	Allocation concealment		The randomization number was then supplied by the system (IVRS). The investigator entered the randomization number into the system (IVRS)."	
2	(selection bias)	Low		
WV1581				
2	Incomplete outcome			
WV1587	data (attrition bias),			
2	symptoms	High	Available data analyzed by ITTI population and non-completers	
WV1581	Incomplete outcome			
2	data (attrition bias),			
WV1587	complications of		Possible effect of oseltamivir on antibody production and complications in the infected subpopulation non-completers	
2	influenza	High		
WV1581				
2	Incomplete outcome			
WV1587	data (attrition bias),			
2	safety data	Low	Based on all participants irrespective of completion status	
WV1581				
2	Selective reporting			
WV1587	(reporting bias), other			
2	bias	High	Outcomes of primary interest for the ITT population	
WV1581				
2				
WV1587				
2	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage not described	
WV1581	Blinding of participants			
2	and personnel			
WV1587	(performance bias), all			
2	outcomes	Low	Matching placebo described	
WV1581	Blinding of outcome	Unclear	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment	

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2	assessment (detection		of treatment group assignment
WV1587	bias), all outcomes		
2			
WV1581			
9			
WV1587			
6	Random sequence		
WV1597	generation (selection		Described as randomised; procedure generating
8	bias)	Unclear	randomisations schedule not available
WV1581			"Randomization was conducted by a central
9			randomisations service via telephone.
WV1587			The investigator or study coordinator telephoned
6			vaccination status and history of COAD, and the tr
WV1597	Allocation concealment		number was then supplied by the centre. The an
8	(selection bias)	Low	in the appropriate place on the subject's Case
WV1581			
9			
WV1587			
6	Incomplete outcome		
WV1597	data (attrition bias),		Available data analysed for both by ITTI
8	symptoms	Low	and ITT populations
WV1581			
9			Possible effect of oseltamivir on antibody
WV1587	Incomplete outcome		production makes the assessment of influenza
6	data (attrition bias),		status and associated complications
WV1597	complications of		in the infected subpopulation non-comparable
8	influenza	High	between the treatment groups
WV1581			
9			
WV1587			
6	Incomplete outcome		
WV1597	data (attrition bias),		
8	safety data	Low	Based on all randomised participants
WV1581			
9			
WV1587			
6	Selective reporting		Outcomes of primary interest to the review
WV1597	(reporting bias), other		are available in the CONSORT-based extraction
8	bias	Low	reconstruction
WV1581			
9			
WV1587			
6			Placebo capsule contained dehydrocholic
WV1597	Other bias	High	acid

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8				
WV1581				
9				
WV1587	Blinding of participants and personnel			
6				
WV1597	(performance bias), all outcomes	Low	Matching placebo described	
8				
WV1581				
9				
WV1587				
6	Blinding of outcome assessment (detection bias), all outcomes	Low	“No open key to the code was available at the study centres, to the monitors, statisticians or at Roche headquarters. In the event of a medical emergency, it was mandatory to properly manage the subject, by the randomisations centre.”	
WV1597				
8	Random sequence generation (selection bias)	Unclear	Described as randomised; procedure generating random numbers	
WV1582				
5				
WV1582	Allocation concealment (selection bias)	Unclear	Inadequate information available to ascertain	
5				
WV1582	Incomplete outcome data (attrition bias), symptoms	Low	Not applicable to the study design (prophylaxis)	
5				
WV1582	Incomplete outcome data (attrition bias), complications of influenza	High	Possible effect of oseltamivir on antibody production; complications in the infected subpopulation non-responders	
5				
WV1582	Incomplete outcome data (attrition bias), safety data	Low	Based on all randomised participants	
5				
WV1582	Selective reporting (reporting bias)	High	Outcome data relating to complications were not reported	
5				
WV1582	Other bias	Unclear	Placebo contained dehydrocholic acid. Dosage not stated	
5				
WV1582	Blinding of participants and personnel (performance bias), all outcomes	Unclear		
5				
WV1582	Blinding of outcome assessment (detection bias), all outcomes	Unclear		
5				