We wish to address several points raised by Adam Jacobs in his February 8, 2013 blog posting "The strange story of the Tamiflu data" (http://dianthus.co.uk/the-strange-story-of-the-tamiflu-data).

We believe our Cochrane review needs to be as robust as possible. Globally, billions of taxpayer money has been spent stockpiling oseltamivir (Tamiflu) and agencies including the CDC which advocate stockpiling have not done an independent evaluation of the extant clinical trial data (http://www.nytimes.com/2012/04/11/opinion/drug-data-shouldnt-be-secret.html). Rigorous independent evaluations of medicines are always important, but especially important given the circumstances surrounding this public health drug.

1. The reasons we did not sign the confidentiality contract Roche proposed in October 2009.

Adam Jacobs writes: "I don't see the need for a confidentiality agreement, so I think Roche behaved badly in demanding one, but I equally don't see the justification for refusing."

Our reasons for refusing are given in Table 2 of Doshi et al. 2012 (http://dx.doi.org/10.1371/journal.pmed.1001201):

> The terms of Roche's proposed contract were unacceptable to us. We declined to sign for two reasons: 1) all data disclosed under the contract were to be regarded as confidential; and 2) signing the contract would also require us ''not to disclose … the existence and terms of this Agreement''. We judged that the requirement to keep all data, and the confidentiality agreement itself, secret would interfere with our explicit aim of openly and transparently systematically reviewing the trial data and accounting for their provenance.

Since October 2009, Roche has not offered us any other contract.

2. What is meant by "full study reports".

Adam Jacobs writes: "I think the reason why the popular narrative seems discordant with what has actually happened is that those claiming that Roche did not make the full reports available are not being very clear about what they mean by 'full reports'."

It is surprising Adam Jacobs had trouble figuring out what we or Roche means by "full reports."

What have specified what is meant by "full study reports" multiple times. In our Cochrane review (http://dx.doi.org/10.1002/14651858.CD008965.pub3) we write:

> In response to the 2009 update of our Cochrane review of NIs in healthy adults (Jefferson 2009a), oseltamivir's manufacturer pledged to make "full study reports" available for the 10 Kaiser treatment trials (Smith 2009). These reports, known as clinical study reports, are unabridged reports of clinical trials generated by trial sponsors primarily as part of submissions to regulators (see Glossary, Appendix 1). An individual clinical study report can be hundreds or even thousands of pages in length, containing far more detail than journal publications.

In Appendix 1, we write:

Clinical study reports. Detailed reports of a clinical trial usually submitted to regulators following a prescribed ICH format. Roche's follow a modular structure (see Appendix 5). Reports can be several hundred pages long and contain details both of the planned design, conduct (protocol), analysis (reporting analysis plan or RAP) and results of the trial.

And “Appendix 6. Example of contents of a Clinical Study Report (from page 1 of WV15670 report)” states:

Final study report modules

This report consists of five modules. Those not supplied in this submission were obtainable from the sponsor on request.

MODULE I: CORE REPORT AND STUDY PUBLICATIONS

Introduction
Rationale
Objectives
Methodology
Efficacy results
Safety results
Discussion/conclusions
Appendices

MODULE II: PRESTUDY DOCUMENTS AND STUDY METHODOLOGY

Protocol and amendment history
Blank CRF
Subject information sheet
Glossary of original and preferred terms
Randomisation list
Reporting analysis plan (RAP)
Certificates of analysis
List of investigators
List of responsible ethics committees

MODULE III: INDIVIDUAL SUBJECT LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA

Demographic data listings
Previous and concomitant diseases
Previous and concomitant medications
Efficacy listings

MODULE IV: INDIVIDUAL SUBJECT LISTINGS OF SAFETY DATA

Laboratory parameters
Vital signs data

MODULE V: STATISTICAL REPORT

In Figure 1 in another article (http://dx.doi.org/10.1136/bmj.d7898) we have given an actual snapshot of the table of contents of a Roche Tamiflu Clinical Study Report in an effort to show what a full report would contain:

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

Roche

5.3.5.4.6 CSR WV15799 (W-144170)

CLINICAL STUDY REPORT MODULES

This report consists of 5 modules.

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

This graphic has been reproduced in a letter from BMJ editor Fiona Godlee to Roche board member John Bell (http://www.bmj.com/tamiflu/roche/rr/611576).

It is clear that in December 2009, Roche promised "full study reports" (http://dx.doi.org/10.1136/bmj.b5374). Here is what Roche wrote:

> As you may be aware, Roche was one of the first companies in the industry to launch an internet site for publishing study protocols and results, in 2005. When the website (roche-trials.com) was created, Roche decided to publish data from 2005 onwards. In view of the exceptional interest in Tamiflu and its key role in the pandemic, Roche has now disclosed (7 December 2009) on roche-trials.com the study summaries (including key data) relating to the Kaiser manuscript. The corresponding full study reports will also be made available on a password-protected site within the coming days to physicians and scientists undertaking legitimate analyses.

3. Should independent reviewers have access to full clinical study reports?

Adam Jabobs writes: "So as far as I can tell, the complaint that Roche have not made 'full' study reports available arises because Roche have made available only the main body of the reports, and not the appendices. To my mind, claiming the full reports are not available is a little misleading, as the main body of the report really should tell you everything you need to know, unless you are are regulator."

We disagree. Regulators and systematic reviewers both aim to do rigorous independent evaluations of trials. Both systematic reviewers and regulators should have access to full study reports, as we have argued (http://dx.doi.org/10.1136/bmj.d7898).

4. What information do we need from full study reports?

Adam Jacobs writes: "So we are left knowing that the Cochrane investigators believe that important information is missing (which seems unlikely if they have access to the main body of the study reports), but they have never specified what information is missing. … So what does the latest Cochrane review itself tell us? Sadly, it doesn't shed much light on this strange state of affairs."

Our review (http://dx.doi.org/10.1002/14651858.CD008965.pub3) makes clear what information is missing, and why it is important.

> Oseltamivir shortens duration of symptoms by less than a day in people with influenza-like illness (ILI) (the intention-to-treat (ITT) population) but there is no evidence of an effect on hospitalisations. However, we found it difficult to draw hard conclusions regarding the other effects of neuraminidase inhibitors on the efficacy outcomes of key importance to this review (viral transmission and complications of influenza). For oseltamivir, many outcomes could not be assessed due to the unavailable of data for the full trial (ITT) population.

Regarding Module 3 (which we do not have access to), we write:

Individual efficacy data are listed under the contents of Module 3. If such data include antibody responses for the complete ITT population we should be able to test our mode of action hypothesis in a definitive way. Individual patient data may also provide the opportunity to present important subgroup analyses, such as the effects of NIs on children. We requested Modules 3, 4 and 5 (the statistical analysis report) from EMA. Of note, for most oseltamivir trials, EMA do not have the relevant documents and neither apparently do National Competent Authorities (email from EMA, 24 May 2011; email from Dutch regulator MEB, 20 July 2011). This means that the modules do not appear to have been either submitted to or requested by regulators, raising questions as to the extent of appraisal of the clinical trials during the regulatory review of oseltamivir in Europe.

Table 12 also summarizes the many analyses we could not perform because we did not have access to full study reports. We have reproduced it here:

Outcome	Data available in clinical study re- port?	Which populations?	Comments
Symptom relief	Yes	ITTI - all clinical study reports have included these data ITT - most clinical study reports have included these data	This outcome is time to FIRST symptom relief
Complications	Yes	ITTI - most clinical study reports have included these data ITT - no clinical study reports have included these data	Events occurring in the first 2 or 3 days not classified as complication Complications only reported for patients classified into ITTI population
Hospitalisation	Yes	These data are included under serious adverse events	Small numbers of patients hospitalised
Harms	Yes	Safety - all clinical study reports have included these data	Neuro-psychiatric events and other events considered related to influenza infection not reported un- less serious
Symptom relapse	No		No data provided in clinical study report Module 1
Drug resistance	No		No data provided in clinical study report Module 1
Viral excretion	Some	ITTI - most clinical study reports have included these data	High proportion of missing data/ data only reported by some centres

		ITT - no clinical study reports have included these data	
Mortality	Yes	All	Only one reported death

To give you an idea how much data we have and do not have, there are 30 trials of oseltamivir (that we know of) eligible for our review. For 13 of those trials we have no data. For 10 trials (those analyzed in the Kaiser 2003 publication in Archives of Internal Medicine), Roche gave us 1 module out of 5 for each of the trials' Clinical Study Reports (CSRs). EMA have given us a second module for the 10 trials as well as the first 2 modules for the remaining 7 trials. That is all the data that EMA holds. In those modules 1 and 2 there is very little useful data on efficacy outcomes because data on the intention-to-treat (ITT) population is generally not provided. Instead almost all comparisons are based on the population that was diagnosed with having influenza infection. We believe this population is not valid because it lacks generalizability and it is not balanced between the treatment groups. There are more placebo patients that made it into this sub-population than oseltamivir patients. The ITT data we need appears to be in module 3 of the CSRs. In addition we have found important discrepancies in the CSRs compared to the corresponding published papers. Also the data we have analysed appear to contradict the reported mode of action of the drug in that it appears to have a symptomatic effect only that is not specific to influenza infection. Therefore we are hopeful that having access to the full CSRs for all 30 eligible trials will allow us to resolve the discrepancies and fully evaluate the mode of action of the drug.

In addition, Module 4 contains individual participant listings of safety data, which may include adverse event reports, especially case cards of serious adverse events. By contrast, Module 1 only contains brief narrative summaries of serious adverse events which can be insufficient for critical assessment by the third parties.

5. Roche has not made full study reports available.

Adam Jacobs writes: "It's important to note that all Roche's trials on Tamiflu have been made available on their website in summary form to anyone, and their clinical study reports have also been made available to the Cochrane investigators. There are probably not many drugs which have been disclosed to systematic reviewers to a greater extent than Tamiflu has."

This table should help make clear what Roche has made available versus what it promised it promised in December 2009 that it would make available "in the coming days":

Table of the ten trials included in Kaiser et al. 2003 review, showing number of modules in the full study report, which modules have been provided to the Cochrane reviewers by Roche to date, and which are being requested.

Trial ID	No of patients	Primary publication of trial	Secondary publication of trial	Number of Modules in the full study report	Modules provided by Roche so far	**We are therefore requesting Modules**

WV15671	629	Treanor et al. 2000.	Kaiser et al. 2003.	5	1	**2,3,4,5**
WV15670	726	Nicholson et al. 2000.	Kaiser et al. 2003.	5	1	**2,3,4,5**
M76001	1459	unpublished	Kaiser et al. 2003.	5	1	**2,3,4,5**
WV15707	27	unpublished	Kaiser et al. 2003.	4	1	**2,3,4**
WV15730	60	unpublished	Kaiser et al. 2003.	4	1	**2,3,4**
WV15812 WV15872	404	unpublished	Kaiser et al. 2003.	5	1	**2,3,4,5**
WV15876 WV15819 WV15978	741	unpublished	Kaiser et al. 2003.	5	1	**2,3,4,5**

Treanor et al. 2000 = Treanor et al. JAMA 2000; 283:1016-24.
Nicholson et al. 2000 = Nicholson et al. Lancet 2000; 355:1845-50.
Kaiser et al. 2003 = Kaiser et al. Arch Intern Med. 2003; 163(14): 1667

(reproduced from http://www.bmj.com/tamiflu/roche/rr/611576)

We note a similarity between Adam Jacobs' statement "There are probably not many drugs which have been disclosed to systematic reviewers to a greater extent than Tamiflu has" And Roche's statement (http://www.bmj.com/tamiflu/roche) "The amount of data already made accessible to the scientific community through our actions extends beyond what is generally provided to any third party in the absence of a confidentiality agreement." (Aug 20, 2010) We have responded to this in Table 2 of Doshi et al. 2012 (http://dx.doi.org/10.1371/journal.pmed.1001201):

> It is irrelevant what is "generally provided". What is relevant is what was promised and the need for public disclosure of clinical study reports.

6. Summary

Adam Jacobs writes: "So it's all very strange that the Cochrane investigators are claiming that they do not have sufficient access to Tamiflu data and that Tamiflu is being used as a poster child for lack of transparency from the pharmaceutical industry."

What is "sufficient access" is subjective, and Adam Jacobs makes clear that he sees no need for sharing "full study reports." We disagree with his position and we have explained why.

What is an objective fact, however, is that "full study reports" have not been provided by Roche, a company that three years ago publicly promised to make such reports available.

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