Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports (Protocol)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

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[Intervention Protocol]

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports

Tom Jefferson[1], Mark A Jones[2], Peter Doshi[3], Chris B Del Mar[4], Carl J Heneghan[5], Rokuro Hama[6], Matthew J Thompson[5]

[1]The Cochrane Collaboration, Roma, Italy. [2]Queensland Health/University of Queensland, Centre for Healthcare Related Infection Surveillance and Prevention/School of Population Health, Brisbane, Australia. [3]Program in History, Anthropology, Science, Technology and Society E51-070, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. [4]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. [5]Department of Primary Health Care, University of Oxford, Oxford, UK. [6]Japan Institute of Pharmacovigilance, Osaka, Japan

Contact address: Tom Jefferson, The Cochrane Collaboration, Via Puglie 23, Roma, 00187, Italy. jefferson.tom@gmail.com. jefferson@assr.it.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To review published and unpublished clinical study reports on effectiveness and harms of NIs for influenza in all age groups (and compare them with our published Review).

BACKGROUND

The protocol will be posted for five months and in this time we will actively seek open feedback and criticism of the methods to be employed. All feedback will be logged and publicly posted (unless privacy is requested), and responded to. In the light of feedback, the protocol may be amended upon agreement of all review authors. Any amendments to the protocol will be detailed in full and along with the reasons why. Feedback can be submitted by email to the corresponding author and via a web-based form on the web site where the protocol is posted.

Description of the condition

Influenza is mostly a mild, self-limiting infection of the upper airways with local (including sniffles, nasal discharge, dry cough, sore throat) and systemic (fever, headache, aches and pains, malaise and tiredness) symptoms. Occasionally patients with influenza develop complications such as pneumonia, otitis media and dehydration, that may be due to effects of the influenza virus itself or associated secondary bacterial infections.

Influenza is not clinically distinguishable from influenza-like illness (ILI) (Call 2005). Influenza in humans is caused by influenza A and B viruses. Currently, influenza A/H1N1 (2009), influenza A/H3N2, and influenza B cause most influenza infections worldwide (CDC 2010).

Treatment remains supportive rather than curative, despite the licensing of a class of antiviral drugs called adamantanes (amantadine and rimantadine) first applied to medicine in the 1960s. Following their use there was widespread viral resistance leading to effectiveness concerns (Bright 2006).

Description of the intervention

Neuraminidase inhibitors (NIs) comprise of inhaled zanamivir (*Relenza*, GlaxoSmithKline) powder, oral oseltamivir (*Tamiflu*, Gilead Sciences and Roche), parenteral *Peramivir* (BioCryst Ltd), inhaled *Laninamivir* (Daiichi Sankyo Co. Ltd, Sugaya 2010) and others still under development (Hayden 2009). The use of NIs has increased dramatically since the outbreak of A/H1N1 (2009) in April 2009, partly because of the rise in amantadine/rimantadine resistance and the lack of an effective vaccine which meant NIs became a widespread public health intervention for early containment and interruption of the virus. The World Health Organization (WHO) had previously encouraged member states to gain experience with NIs (WHO 2004).

How the intervention might work

Although NIs may reduce the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006), their effectiveness is thought to lie in their ability to inhibit neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005). Oseltamivir phosphate (OP), *Tamiflu,* is the prodrug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE). OT may induce hypothermia (Ono 2008) possibly due to a central depressant action (Hama 2008). NIs may also inhibit human sialidase (Li 2007) thereby causing abnormal behaviour.

Any treatment that reduces the excretion of virus from infected people might be a useful public health measure to contain an epidemic. In addition to symptomatic treatment, prophylactic use for interrupting the spread of disease has informed pandemic planning over the past decade.

Why it is important to do this review

Most attention has been focused on oseltamivir because it is not just used as a prescription drug for patients suffering from influenza: on the recommendation of the WHO (WHO 2010) it has been purchased and supplied globally (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009). Governments spent billions of dollars stockpiling it as a public health measure. The WHO has recently also recommended it be added to the list of essential medicines (WHO 2010) and oseltamivir has been prescribed for the treatment of influenza worldwide after the outbreak of 2009 A/H1N1 influenza and the pandemic declaration by the WHO (WHO 2009). Oseltamivir has been prescribed far more than other NIs, most likely because of its ease of administration and storage.

There are some suggestions that NIs may not be as safe as previously assumed, with associations between oseltamivir use and neuropsychiatric adverse reactions, particularly, including sudden death (Hama 2008).

An earlier version of this Cochrane Review in adults, we found that NIs were effective in reducing symptoms and complications (Jefferson 2006). However, criticisms of that review led to doubts about their effectiveness against complications (Jefferson 2009a; Jefferson 2010a). Since then, doubts remain about the effectiveness and safety of the drug because its evaluation has been limited to manufacturer-sponsored trials. There is clear evidence of publication bias (see below), and there is concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009).

In response to the most recent update of our Cochrane Review of NIs in healthy adults (Jefferson 2009a), oseltamivir's manufacturer pledged to make "full study reports" available for 10 treatment trials, of which eight have never been published (Smith 2009). This protocol explains the rationale behind our current efforts to re-update our review in the light of this potential source of data and of regulatory documents, either openly sourced or obtained under

the US Freedom of Information Act. This review is the amalgamation of two long-standing Cochrane Reviews on the effects of NIs for influenza in healthy adults (Jefferson 2009a; Jefferson 2010a) and children (Matheson 2007; Shun-Shin 2009). Publishing updates of the Cochrane Reviews of NIs in both children and adults generated intense interest from clinicians and the media during the influenza outbreak declared a pandemic by WHO in 2009. The Cochrane Review of NIs in healthy adults highlighted the presence of publication bias (Jefferson 2010a). Obtaining clinical study reports may allow us to clarify the effects by age because some trials report adult and paediatric outcomes.

As with most systematic reviews, our previous work included evidence identified by comprehensive searches of literature databases (such as PubMed) of published randomised, placebo controlled studies. This is designed to ensure that reviews are based on the highest quality, relevant evidence. In addition (and in line with common practice) we requested randomised controlled trials (RCTs) from authors of published trials (who may have undertaken other trials) and experts and manufacturers that had *not* been published. This harvested excerpts of eight unpublished and two published treatment trials with oseltamivir. However, we encountered discrepancies between the published trials and unpublished excerpts. Our attempts to reconcile these by contacting the pharmaceutical manufacturer and study authors failed (the latter were unable to provide us with the necessary data: some were not in possession of the data; others may have been restricted by confidentiality agreements). In addition, we ascertained that ghost writers had been involved (Cohen 2009), which means the named authors may not have been in full control of the trial publications. We have also identified several key differences in licensed indications for oseltamivir between regulatory systems (mainly between the US, Europe and Japan) and under-reporting of harms (Doshi 2009). This undermined our confidence in published data and in the findings of our previous Cochrane Reviews.

To update the amalgamated reviews we are attempting to identify all relevant trials (that is, unpublished as well as published) and extract data from full clinical study reports (CSRs), a more detailed source of information than published journal articles. We know that this will be a more laborious process but we believe that the amalgamation of the two Cochrane Reviews (Jefferson 2010a; Matheson 2007) will make this process more efficient by sharing expertise and time in extracting and assessing data from these sources.

Examples of discrepancies and publication bias

The two most cited published trials of oseltamivir either do not mention serious adverse events (Nicholson 2000), or state that "... there were no drug-related serious adverse events" (Treanor 2000). This finding has been repeated by bodies such as the UK National Health Service (NHS) ("No serious adverse events were noted in the major trials and no significant changes were noted in laboratory parameters") (UKMIPG 2001). However, they are inconsistent with relevant information from CSRs Module 1 content released to us by Roche in January 2010. The CSRs Modules 1 report 10 serious adverse events (in nine participants) in the two trials, three of which were classified as possibly related to the study drug (oseltamivir). It has also emerged that 56% (2691/4813) of patient data from randomised, placebo controlled trials have never been published. Exclusion of unpublished data changed our previous findings regarding oseltamivir's ability to reduce complications of influenza (Doshi 2009; Jefferson 2009a).

A modified approach

To resolve inconsistencies and under-reporting, we are changing our approach by no longer including trial data as reported in papers published in biomedical journals. Instead, we are treating clinical study reports (CSRs) as our basic unit of analysis (the original and unabridged record of trials, short of individual patient data). CSRs are often sent to national drug regulators such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA), which require more stringent standards for completeness and accuracy of reporting than biomedical journals.

Unfortunately, most CSRs go unpublished and are not readily available for wider scientific scrutiny, despite calls to make all relevant trial data public (Godlee 2009) and the known problems with reporting biases (McGauran 2010).

However, in the case of NIs, Roche, the manufacturer of oseltamivir, has pledged to make some of its full study reports available (Smith 2009) and expressed in email correspondence a willingness to consider making study reports for additional trials available as well. GSK have given a similarly positive response to our enquiries. We have also contacted BioCryst Ltd, makers of peramivir, and are in the process of contacting Daiichi Sankyo, makers of laninamivir, the newest NI, for similar information.

Therefore, in this review, we are modifying our approach. We will analyse unpublished reports only, which should enable us to address the remaining questions about the effects of NIs using the most complete data set short of individual patient data. We have requested the original CSRs from the manufacturers and will review additional, apparently unpublished trials we have since identified. At present, Roche has only provided us with partial CSRs: one module of the four to five contained in each CSR (Appendix 1) for 10 oseltamivir treatment trials. The other modules are likely to contain key information such as the protocols with the list of amendments and original reporting analysis plans. Regardless of success with our requests to obtain full CSRs, we intend updating our Review with available material and subsequently update it as and when additional data become available.

In addition to seeking CSRs, we will read and review regulatory documentation. Although no CSRs are obtainable from regulators, important information regarding trials which are either unpublished or supplementary details to CSRs of available trials are often contained in regulatory documents. Unlike us, regulators have access to the whole data set.

Implications

This modified approach to a Cochrane Review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about NIs for influenza.
Our Cochrane Review should contribute transparent and independent information to a European regulatory and pharmacovigilance legal framework which commentators declare to be weak (Cohen 2009; Godlee 2009). We believe that as NIs have become public health drugs, recommended and stockpiled globally, independent scrutiny of all the evidence relating to harms and effects on complications is necessary to provide a complete and unbiased view of their performance.

Implication for novel H1N1 influenza

In response to our December review (Jefferson 2009a; Jefferson 2010a), some have argued that its findings cannot be applied to A/H1N1 (2009), suggesting that it is a new virus and thus we need new evidence (JAID 2010; Maugh 2009; Nebehay 2009; NHS 2009; NHS 2010). We disagree. If the treatment and prophylaxis of novel A/H1N1 influenza were a new indication for which past clinical trials were inapplicable, the mass administration of oseltamivir over the past year would constitute off-label use. However, there is little reason to believe this is the case. Novel A/H1N1 is a new strain of a subtype that has been circulating since 1977, but it also resembles A/H1N1 strain that has been circulating before 1957 (CDC 2009) or before the 1918 pandemic (Itoh 2009). Influenza subtype A/H1N1 was indeed circulating in the clinical trials we have included in our previous Reviews. In addition, oseltamivir and zanamivir were approved by regulators worldwide for the treatment and prevention of influenza types A and B, not specific subtypes or strains of influenza A and B. The expectation of regulatory approval is thus that the effects of these drugs demonstrated in clinical trials will apply to future strains of influenza A and B. Use of these drugs during the pandemic was not off-label, but legal because of the assumption that the clinical trial evidence underpinning regulatory approval applied to novel A/H1N1. We intend to review the clinical trial evidence with the expectation that our results, similar to regulators, will apply to novel influenza A/H1N1 as well.

Wider implications

The modified approach in this Cochrane Review may provide a justification for widespread adoption of this type of method to systematic reviews of interventions. Our independent scrutiny of NI benefits and harms using all possible trial information may inform the debate on the adequacy of existing regulatory frameworks in the adoption of new drugs and whether other systematic reviews should move to this new more rigorous approach which focuses on trial programmes rather than single trials (Eyding 2010; Ioannadis 2010). We will discuss the implications of using published or unpublished clinical study reports in compiling systemic reviews. Although there is substantial evidence for the effects of reporting bias in estimates of effectiveness, less is known of its impact on the evidence of harms (Chou 2005). We intend to quantify the additional resources required to follow our novel approach. This entails a review of time and resources that made it possible to carry out this review. This may shed light as to the feasibility of other systematic reviews to proceed in a similar fashion. We intend to speculate on the generalisability of our approach to other disease areas in which a greater number of manufacturers and non-commercial investigators are active (Eyding 2010; Ioannadis 2010)

OBJECTIVES

To review published and unpublished clinical study reports on effectiveness and harms of NIs for influenza in all age groups (and compare them with our published Review).

METHODS

Criteria for considering studies for this review

Types of studies

We will include evidence from RCTs testing NIs effect for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza.

Types of participants

Previously healthy people (children and adults). 'Previously healthy' will be defined as including chronic illness (such as asthma, diabetes, hypertension) but excluding illnesses affecting the immune response (such as cancer, AIDS). We will use the same definitions as used in nearly all influenza RCTs and include only trials on people exposed to naturally occurring influenza with or without symptoms.

Types of interventions

NIs by any route compared with placebo or standard care during on and off treatment (on-t and off-t) periods.

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment studies.

1. Symptom relief.
2. Hospitalisation and complications.

3. Harms.

Primary outcome measures for prophylaxis studies.

1. Influenza (both symptomatic and asymptomatic, and laboratory-confirmed) and influenza-like Illness (ILI).
2. Hospitalisation and complications.
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts).
4. Harms.

Secondary outcomes

Secondary outcome measures for treatment studies.

1. Symptom relapse after finishing treatment.
2. Drug resistance.
3. Viral excretion.
4. Mortality.

Secondary outcome measures for prophylaxis studies.

1. Drug resistance.
2. Viral excretion.
3. Mortality.

We will examine listed secondary outcomes, although recognising that these may be less relevant, less reliably measured, or analysed with multiple statistical tests (leading to inflation of the overall significance level). Some trials we have reviewed so far had insufficient power to detect an effect on mortality.

We will pay particular attention to complications and adverse events, including 'compliharms', (outcomes which may be classified as either harms or complications), as this is where evidence is currently scarce or inconclusive (Jefferson 2009a; Shun-Shin 2009). Our initial examination of some regulatory documents and some published versions of the studies, has identified that some symptoms and sequelae of influenza (such as pneumonia) are variously classified as a 'complication of influenza' or as an 'adverse event of the treatment' (Appendix 2). In post-exposure prophylaxis (PEP) trials we will focus on evidence of interference with viral transmission.

Extracting 'compliharms' may be difficult in the Roche trials because adverse events are reported for *all* participants while complications are only reported for *infected* participants. Hence we may have to assume complications in non-infected participants are equally likely in treatment and control groups if we have no access to those events (that is, the numerator will be an underestimate).

Search methods for identification of studies

A single, up-to-date and complete list of all clinical trials conducted on humans using a given drug is rarely available in the public domain. Such a list can be constructed using multiple, cross-referencing methods. In addition, because the majority of clinical trials of a given drug are fully funded or sponsored by the drug's manufacturer, manufacturers can be contacted to help ensure the accuracy and completeness of such a list.

To ensure the list does not include duplicate entries, it is important to assign each trial a Unique Trial ID. 'Author' is not a good choice of Unique Trial ID as different authors can be present across different versions of the same trial (that is, the authors of unpublished CSRs can be different from publications arising from the same clinical trial). Nor is 'publication' a good option for Unique Trial ID because not all studies are published. Some trials will have company specific codes and some will have public clinical trial registry numbers, or both or neither.

The majority of trials in our study are manufacturer funded (with corresponding manufacturer protocol IDs), and accordingly we have used the manufacturer protocol ID as our Unique Trial ID. Best efforts to ensure accuracy can still leave uncertainties that may require further correspondence for clarification (for example, the difference between WV15673 and WV15673D).

We are constructing a list beginning with clinical trials identified from previous Review updates. To this, we are adding additional trials in humans identified from multiple sources, such as manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents, and public and manufacturers' registers (Burch 2009; Cooper 2003; Jefferson 2006; Tappenden 2009; Turner 2003). These include reference lists of single or synthesis clinical trials, HTA documents, FDA medical reviews, a review by Kaiser (Kaiser 2003), the EMEA scientific discussion, material sent to us by Roche for our 2009 update, Roche's and GSK's submissions to UK National Institute of Clinical Excellence (NICE), Japanese regulatory new drug applications, registries such as ClinicalTrials.gov and www.roche-trials.com, and other documents. We also plan to conduct traditional database searches (search strategy defined below) and searches of grey literature to identify previously unknown trials.

For each trial, we will attempt to gather the following details to enable decision-making regarding whether the trials meet our inclusion criteria:

- Unique Trial ID
- Other IDs
- Phase of study
- Sponsor
- Short description
- Official Trial title
- First authors (name and email)
- Type of trial
- Comparator
- Outcomes assessed
- Date of trial
- Study period (days)
- Population
- Number of subjects planned
- Number subject enrolled

- Number subject completing
- Trial status (for example, completed, ongoing, or early termination)
- Publication status (a citation or understanding of why it was not published)
- How identified (to record how the trial was discovered)
- Notes

We will enter identified studies into a spreadsheet (part of Tool D - see below). We will submit a draft list of clinical trials to manufacturers asking for their cooperation in checking the accuracy and completeness of its content. We plan to assign three categories to identified trials once we have our complete list:

- definitely included;
- definitely excluded; and
- trials for which we need further information.

Where further information is required, it will be requested from the trials' sponsor and/or first/corresponding author.

Electronic searches

We will update our searches of the electronic databases of published studies previously carried out for the Cochrane Reviews on NIs in children (Matheson 2007) and healthy adults (Jefferson 2010a). The purpose of the searches is to identify trials previously unknown to the review authors, but no published material for any trial will be analysed for this review. Rather the *unpublished* data from them will be analysed instead.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* latest issue) which includes the Acute Respiratory Infections Group's Specialised Register, the Database of Reviews of Effects (DARE) and the NHS Health Economics Database, MEDLINE (1966 to present) and EMBASE (1974 to present).

The following search strategy will be used to search MEDLINE and CENTRAL. The MEDLINE search will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (Lefebvre 2011). The search strategy will be adapted for EMBASE. There will be no publication or language restrictions.

MEDLINE (Ovid)

1. Influenza, Human/
2. exp Influenzavirus A/
3. exp Influenzavirus B/
4. (influenza* or flu).tw.
5. or/1-4
6. Oseltamivir/
7. Zanamivir/
8. Peramivir/
9. Laninamivir/
10. neuraminidase inhibitor*.tw.
11. (oseltamivir or zanamivir or tamiflu or relenza or peramivir or laninamivir or gs4071).tw,nm.
12. or /6-11
13. 5 and 12

Searching other resources

See Search methods for identification of studies section.

Data collection and analysis

Selection of studies

Four review authors (TJ, CH, MJ, RH) will independently read all data relating to the studies on the list constructed during our search and select studies fulfilling our inclusion criteria. One review author (PD) will compile the assessments into a single sheet for CDM. Disagreements will be resolved by discussion with another review author (CDM).

We will then request full internal CSRs (minus participant identification) for each trial that is definitely included.

Data extraction and management

We intend conducting a two stage exercise. In the first stage we shall assess the reliability and completeness of the identified trial data. Only reliable and reasonably complete data will be included in the second phase of the review, which is an analysis following standard Cochrane methods.

Stage 1

Two review authors will separately extract data from the same CSR for studies included in stage 1 of the review. The review authors will independently extract data from each of the sources where we have more than one type of study report on the same trial from different sources (for example, a trial report submitted to a regulatory body and a trial report from a pharmaceutical company) and then compare the results. We will record and tabulate disagreements between data extracted from the same source and between different sources. We will extract data using a modified CONSORT statement extraction template (Appendix 3).

The modified CONSORT reconstruction template aims to assemble a concise version of the CSR which will include all important methods as well as define and extract all relevant outcomes. The CONSORT template includes the features that would be expected to be found in a published trial report but in greater detail. It does not include introduction or discussion sections. The following will be extracted for each trial.

1. Background and objectives.
2. Methods: including trial design, important changes to methods after trial commencement (such as eligibility criteria), with reasons.

3. Participants: including eligibility criteria for participants and settings and locations where the data were collected.

4. Interventions: the interventions for each group with sufficient details to allow replication, including how and when they were actually administered.

5. Outcomes: pre-specified primary and secondary outcome measures, including how and when they were assessed and changes to trial outcomes after the trial commenced, with reasons.

6. Sample size: how it was determined and explanation of any interim analyses and stopping guidelines.

7. Randomisation: including sequence generation and method used to generate the random allocation sequence.

8. Blinding: who was blinded after assignment to treatment groups.

9. Statistical methods: methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses.

10. Results: participant flow, numbers of participants randomly assigned, losses and exclusions after randomisation, together with reasons. Baseline demographic and clinical characteristics for each group

11. Outcomes: primary and secondary outcome results for each group.

12. Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory.

13. Harms: all important harms or unintended effects in each group.

One review author will complete the reconstructed CONSORT template in full (Appendix 3) with the name and date of completion, a statement of conflict of interests. A second review authors will check the template. These reconstructed templates will be made available for scrutiny upon publication of the full review. We will copy extracted data, text, tables and figures directly from the relevant sections of the CSR into the appropriate section of the template. We will not change the text in any way apart from clarifying abbreviations, spellings etc, and aside from highlighting text. We will use three types of text highlighting in the document.

Yellow: will be used where text, figures or tables need to checked with further information (for example, if an adverse event is referred to in an appendices or a further CSR module).

Red: where text or comments have been inserted by one or both review authors but require an additional opinion due to concerns that there is the potential for discrepancies in the CSR.

Green: any text or tables of our own we have added to the template (for example, a reconstructed table of adverse events).

Two review authors have piloted the reconstruction method on Roche oseltamivir trial WV15671 with data from the CSR Module 1 from Roche and data submitted to UK NICE. The pilot reconstruction has been discussed amongst the whole group for clarification. Two review authors will judge the reliability and completeness of each reconstructed trial. A third review author will act as arbiter and will have the casting vote regarding the inclusion of the trial in Stage 2. Each reconstruction will be assessed using information from regulatory sources.

We have devised four types of repository extraction, management and cross-referencing tools for the data and information retrieved and collated during the review due to the complexity of the work.

Tool A is a table of content (TOC). The TOC is a common resource, to be used as a formal directory or index, listing the location, by page number, where specific clinical trials are cited in primary documents the review team has access to and is included in the current review. The TOC primarily indexes regulatory documents (notably medical, pharmacological and statistical reviews written by the US FDA); it does not at present include EMEA reviews. The TOC is kept as a spreadsheet. The last sheet in the TOC lists CSRs the review team has access to, their provenance and degree of completeness (partial or complete). To identify information within and across documents, which are thousands of pages in length, we have used the trial ID to plot which trials are cited where in our database of regulatory and company data. Review authors assigned to a specific trial could do their own searches within regulatory material looking for mention of that trial, but there is a risk that without an index, they would miss relevant sections. This may occur for several reasons. Firstly, not all regulatory material may be searchable (by being transformed by 'optical character recognition' software); only somebody reading the documents serially would find relevant trial references. Secondly, reference to trials is inconsistent; trial WV15671 may be at times referred to as "WV 15671" or even "15671". Again, without somebody reading through the documents serially, finding all references to a specific trial may be difficult even within searchable documents.

Tool B is the TOC evidence (TOCE). TOCE is a version of the TOC with annotations. It is based on the TOC but has an added brief description of the content of each regulatory and pharmaceutical files available to us.

Tool C is a narrative of our review, documenting the evolution of methods and detailed summary of the information contained in the FDA and other regulatory documents. This document is intended as a detailed record of the project with dates as well as a source of information on the topic.

The rationale for the creation of three different tools lies in the complexity of our undertaking. We are engaged in the assessment of the completeness and reliability of the data in trials X, Y, Z and sub trial programme Q (i.e. prophylaxis for NI R). To do this we have to use all information at our disposal. This includes information on the design, methods and results of trials - but also the comments of those who had access to the full registration trial programme, notably regulatory agencies. We hope that their critiques will tell us things which are invisible to those not having access to full CSRs and the myriad attendant documents that go with trials. (The Roche submission to FDA for oseltamivir for the

treatment of influenza in those aged 13 and above was over 300 volumes in length).

Finally, we have created a central reference resource holding details of correspondence, the definitive frame of studies with referencing to other study identifiers (published or semi-published versions, company ID numbers), progress notes, lists of authors, relevant researcher, decision makers and pharmaceutical spokespeople quotes and other information fragments identified during the review (Tool D). We also have a central, password-protected electronic repository where all tools and published and unpublished studies, reviews, HTA and regulatory or pharmaceutical documents are stored.

Assessment criteria. Assessment as to eligibility for trials to move to Stage 2 will be based on the following three criteria:

1. Completeness. CSR/unpublished reports includes both identifiable CONSORT-specified methods to enable replication of the study. Identifiable CONSORT-specified results (primary outcomes, tables, appendices)
2. Internal consistency. All parts of the same CSR/unpublished report are consistent.
3. Validated data trial details and outcome measures will be cross-checked against regulatory documents, other versions of the same CSR/unpublished reports, other references.

Consistency checks will be applied. where inconsistencies occur. They will be discussed or clarified with original trialists, manufacturers, or study guarantor/principal investigator(s).

A decision on whether a trial moves to Stage 2 will be reached by consensus. When consensus is not possible and cannot be reconciled, dissent will be reported.

Stage 2

This will be based on standard Cochrane methods for extracting, appraising and synthesising the evidence (with two review authors independently extracting data, with a third review author arbitrating). Data will be extracted onto standard forms, checked and recorded.

Assessment of risk of bias in included studies

Once stage 1 is completed, we will assess risk of bias using established criteria (Higgins 2011) in single studies. We will also test for the presence of potential biases across the entire trial programme of each NI using a multi-level assessment framework formulated as a series of 30 null hypotheses (Additional tables). Previous studies comparing regulatory with published or internal company sources of evidence have reported a variety of different biases that affect medical knowledge (Chou 2005; MacLean 2003; McGauran 2010). We expect that our access to multiple sources for the same trial data set will aid us in assessing the presence, direction and impact of one or more of these reporting biases, some of which have already been discovered in the oseltamivir data set (i.e., publication bias). Due to the laborious and iterative nature of the assessment, we have prioritised the null hypotheses to be tested into first (Table 1) and second rank (Table 2) according to the potential impact of each type of bias on our conclusions and of knowledge of the effects of NIs. Methodological risk of bias assessment will be carried out using the *Cochrane Handbook for Systematic Reviews of Interventions* criteria (Higgins 2011).

Measures of treatment effect

All analyses will use the intent-to-treat (ITT) population as it is the most methodologically rigorous and clinically relevant. Our intention is to express the results of our analyses both as absolute and relative measures and estimate the likelihood and impact of bias on our conclusions. Assessment of bias on this scale will be done for the whole trial programme rather than for each trial, as recently recommended by Ioannidis (Ioannadis 2010) and outlined above. We will use the tri-dimensional dose-relatedness, timing and patient susceptibility (DoTS) methodology to assess likelihood of harms causality (Aronson 2003).

Based on pharmacokinetic, toxicokinetic data and the comprehensive nature of oseltamivir we will review harms evidence in two time frames. In time frame 1 we will assess intermediate reactions (occurring after some delay) to oseltamivir carboxylate/zanamivir such as infection, renal toxicity, hyperglycaemia/diabetes haemorrhage and general weakness (Aronson 2003). These may be closely linked to drug efficacy. In time frame 2 we will assess the first dose/early reactions to unchanged oseltamivir. This is the review for pure adverse effects. First dose reactions occur after the first dose (or on the first day) of a course of treatment and not necessarily thereafter. Reactions occurring early in treatment may abate with continuing treatment as the participants develop tolerance (Aronson 2003), or as a result of interaction with the infection (Hama 2008). In addition we will analyse harms by on time frame periods and off time frame periods.

We will report risk ratios (RR) or hazard ratios, absolute risks (risk differences and numbers need to treat), treatment harms (numbers needed to harm) and treatment effects to ensure clear interpretation of the drugs' benefits and harms.

We will present estimates of effect as data for three broad age groups: children, adults, and the elderly, where relative and absolute benefits and harms may differ. We will present data separately for prophylaxis, post exposure prophylaxis (PEP) and treatment studies.

Unit of analysis issues

We expect the majority of trials to randomise at the patient level and events to only occur at most once in a participant. However, in the case of multiple events per participant, we will consider analyses that compare incidence rates in the two groups such as

Poisson and Negative binomial regression. In the case of cluster randomised trials (for example, households rather than individuals are randomised) we will include data from analysis either at the household level or at the participant level if the effect of clustering has been taken account of appropriately (for example, by using hierarchical modelling techniques).

Dealing with missing data

We have developed a comprehensive strategy for dealing with data which we know are missing at the trial level, i.e. unpublished trials (see Search methods for identification of studies section).
At the participant level (i.e. within a trial) we will consider not including a trial if the amount of missing data is large (for example, > 20%) or if missing data is in different proportions in the treatment and control groups or if all participants are not accounted for in the reporting of the analysis. We will also consider the impact of including or excluding trials with potentially unreliable results due to missing data issues in a sensitivity analysis.

Assessment of heterogeneity

We will use the I^2 statistic to measure the level of statistical heterogeneity for each outcome (Higgins 2011) and test for heterogeneity using Cochrane's Q chi^2 test.

Assessment of reporting biases

This will be based on the empirical framework in Table 1. Biases will be assessed depending on available data and order of priority. For example, the results of the testing of the overarching hypothesis (presence of reporting bias) will take place on the basis of the data currently available and will be revised each time new data are obtained. Equally, the second null hypothesis (testing for analysis plan differences between the study protocol and the full study) will be tested if the modules containing the protocols have been released to us. We aim to eventually assess the remaining potential biases in both tables and compare clinical study reports from unpublished data with those published (that is, within current Reviews).

Data synthesis

When there is substantial heterogeneity (I^2 statistic > 50%) we will consider possible explanations for this and consider not combining results. We will use a sensitivity analysis when necessary to investigate the contribution of individual trials to any heterogeneity. Whether or not heterogeneity is detected, we will perform a random-effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety). More specifically, the DerSimonian & Laird method will be used. Note that in the case of zero cells (for example, no events in one group) 0.5 will be added to each cell of the 2 × 2 table for any such study.
We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) (Parmar 1998) to enable meta-analysis of time to event outcomes. Due to concerns that time to event outcomes may violate proportional hazards assumptions, we will also consider analysis of this outcome as a continuous outcome noting that the data are likely to be skewed. We will use the inverse-variance random-effects method for this analysis.

Subgroup analysis and investigation of heterogeneity

We will attempt to carry out a subgroup analysis by type of NIs and age group, specifically comparing effects of NIs in children (up to the age of 12 years), adolescents (13 to 17 years), adults (18 to 64 years) and the elderly (65 years and onwards) in which relative and absolute benefits or harms may differ. To avoid selective reporting we will conduct analyses to be consistent with what is pre-specified in the trial study reports. Any additional analyses will be reported as "post-hoc".

Sensitivity analysis

We will carry out a sensitivity analysis of methods, comparing our results obtained using fixed-effect and random-effects models. The Mantel-Haenszel method will be used for fixed-effect analysis except in the case of sparse data, in which case Peto's method will be used (as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*). We also intend carrying out a sensitivity analysis of our results by publication status (published trials versus regulatory submissions versus CSRs) to assess the extent to which publication status and source of data affect results, by funder and study quality.
Finally, we will compile and populate data tables showing data and conclusions from different studies and different regulator sources. We aim to reconcile any differences by contacting manufacturers and regulators, and formulating a series of questions based on any documented discrepancies.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. First priority null hypotheses to test.

Null hypothesis	Definition	Potential Impact	Framework to test hypothesis

Table 1. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. First priority null hypotheses to test. (*Continued*)

There is no under-reporting (overview hypothesis) (Hopewell 2009; McGauran 2010)	Under-reporting is an overall term including all types of bias when there is an association between results and what is presented to the target audience	Tailoring methods and results to the target audience may be misleading. The direction of the effect could change or the statistical significance of the effect could change or the magnitude of the effect could change from clinically worthwhile to not clinically worthwhile and vice versa	1. Is there evidence of under-reporting? 2. What types of under-reporting are apparent (list and describe them)? 3. What is the overall impact of the under-reporting on the results of a meta-analysis (compare estimates of effects using (under)reported data and all data)? 4. What is the impact of under-reporting on the conclusions of a meta-analysis i.e. are conclusions changed when all data is reported?
There is no difference between analysis plan in the protocol and final report (or the differences are listed and annotated) (McGauran 2010)	When protocol violations especially if not reported and justified, are not associated to study results	Post hoc analyses and changes of plan lead to manipulation of reporting and choice of what is and not reported	1. List any discrepancies between what is pre-specified in protocol and what was actually done 2. Can these discrepancies be explained by documented changes or amendments to the protocol? 3. Were these changes made prior to observing the data? 4. What is the perceived impact of these changes on the results and conclusions?
There is no difference between published and unpublished conclusions of the same study (McGauran 2010)	A specific bias relating to the selective reporting of data in association with target audience	Results have been tailored to the intended recipient audience	1. Compare reporting of important outcomes (harms, complications) between published reports and other reports such as those to regulatory bodies e.g. FDA 2. Document any differences in conclusions based on separate reports of the same studies
Presentation of same data set is not associated with differences in spelling, incomplete, discrepant, contradictory, or duplicate entries (Doshi 2009; Golder 2010; Jefferson 2009a)	Different versions of the same data set are associated with discrepancies	Raises questions of whether these discrepancies are mistakes or deliberate?	1. Document any differences or similarities in separate reports of important outcomes (harms, complications) based on the same studies 2. Report any discrepancies to

Table 1. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. First priority null hypotheses to test. (*Continued*)

			the manufacturer and ask them to clarify and correct any errors 3. What is the impact on the evidence base of including or excluding material with similar discrepancies?
There is no evidence of publication bias (Hopewell 2009; McGauran 2010)	Publication status is not associated with size and direction of results	Negative or positive publication bias can have major impact on the interpretation of the data at all levels especially	1. Are there studies that have not been published (yes/no)? 2. How many studies have not been published (number and proportion of trials not published and proportion of patients not published)? 3. Construct a list of all known studies indicating which are published and which are not 4. What is the impact on the evidence base of including or excluding unpublished material?
There is no evidence of outcome emphasis bias (McGauran 2010)	When over or under emphasis of outcomes is not associated with size or direction of results	Can lead to wrong conclusions because over emphasis on certain outcomes	1. Are all of the pre-specified outcomes in the study protocol reported? 2. Are the outcomes reported in the same way as specified in the study protocol? 3. Are there any documented changes to outcome reporting listed in the study protocol? 4. What is the impact on the evidence base of including or excluding emphasised outcomes?
There is no evidence of relative versus absolute measure bias (McGauran 2010)	When choice of effect estimates is not associated with size or direction of results	Can lead to wrong conclusions because of apparent under or overestimation of effects (e.g. in the use of relative instead of absolute measures of risk)	1. Are both relative and absolute measures of effect size used to report the results? 2. Is the incidence of each event reported for each treatment group? 3. What is the impact on the evidence base of including estimates of effect expressed either in relative and absolute measures?

Table 1. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. First priority null hypotheses to test. (*Continued*)

There is no evidence of follow up bias (McGauran 2010)	When there is no evidence that length of follow up is related to size and direction of results	Can lead to wrong conclusions due to over or under emphasis of results	1. Are reported results based on the complete follow up of each patient? 2. Are important events (harms, complications) unreported because they occurred in the off-treatment period? 3. What is the impact on the evidence base of including or excluding material with complete follow up?
There is no evidence of data source bias (Chou 2005; McGauran 2010)	There is no difference between the evidence base presented to regulators (for approval for an indication) and that produced by or in possession of drug's the manufacturer (Chou 2005)	Can lead to approved indications inconsistent with full data set	1. Have regulators been presented with all data sets resulting from trials sponsored by the drug's manufacturer? 2. Have all national regulatory agencies been presented with the same trial data sets? 3. Can differences between national regulatory agencies be explained by access to different data sets?

FDA: Food and Drug Admnistration

Table 2. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. Second priority null hypotheses to test.

Null hypothesis	Definition	Potential impact	Framework to test hypothesis
There is no difference by funder (Jefferson 2009b; McGauran 2010)	When results and tone of conclusions are associated with type of funder	Funder influences results, conclusions and study visibility	1. Are there substantial numbers of comparable trials with different funding? 2. Is type of funder associated with quality, relationship between conclusions and data presented and prestige of the journal of publication? 3. Is the type of funder associated with publication status?
There is no evidence of authorship musical chairs bias (Cohen 2009; Doshi 2009; Jefferson	When different authors for the same data set are presented to different target audiences	Raises an accountability question: who is responsible for the study?	1. Are the names of the people responsible for the unpublished report the same as those of the

Table 2. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

2009a; MacLean 2003)			published reports? 2. Is the responsibility for conducting the trial clear?
There is no evidence of time lag bias (McGauran 2010)	When result reporting time frame is not associated with size or direction of results	Can lead to wrong conclusions	1. Are there significant differences in on-t and off-t treatment data? 2. Does the reporting or not reporting of on-t and off-t treatment data impact on the conclusions?
There is no evidence of location bias (Higgins 2011)	The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results	Can lead to wrong conclusions in a specific setting or mislead generalisation to another context	1. Is there an association between publishing trials in journals with similar ease of access and data basing and size or direction of results? 2. How does this relate to unpublished material?
There is no evidence of disclosure pressure bias (McGauran 2010)	When external stimuli to publish or not are not associated with size or direction of results	Can lead to wrong conclusions because of blocks on what is reported or not	1. Why were some data and/or studies not published? 2. What impact do these motives have on interpretation of the evidence base?
There is no evidence of off-label bias (McGauran 2010)	When reporting is not associated with a higher or lower probability of unregistered indications use or recommendations thereof	Can lead to wrong conclusions because of reporting of data which leads to off label use or is a product of off label use	1. Is there any difference in the on label indications and dosage between published and unpublished clinical study reports? 2. If so, how does the inclusion or exclusion of off label data impact conclusions from the evidence base of this drug?
There is no evidence of commercial confidentiality bias (McGauran 2010)	When commercial confidentiality rules do not impact on presentation of results	Can lead to wrong conclusions because IPR or commercial confidentiality prevent full disclosure of results	1. Is there evidence of commercial confidentiality being invoked for the decision to publish or otherwise. 2. If so, how do the inclusion or exclusion of commercial confidentiality restricted data impact conclusions from the evidence base of this drug?
There is no evidence of inclusion of previously unpublished data bias (Golder 2010;	When there is no evidence of inclusion of heterogeneous unpublished data of variable	Can lead to wrong conclusions because of the inclusion of biased data not clearly identified	1. Is there any evidence of published review studies (particularly meta-analyses) containing

Table 2. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

McGauran 2010)	quality and sometimes difficult to interpret either because of swamping or absence of methods chapters	as such	previously unpublished data? 2. If so what is the impact of including or excluding unpublished data on the conclusions from the evidence base of this drug?
There is no evidence of blank cheque bias	When there is no evidence that third-party independent researchers agree to having a trial's sponsor fill in their data extraction sheets for unpublished data	Can lead to wrong conclusions because of the impossibility of independently assessing data. If the practice is not declared, it can mislead readers, giving conclusions a spurious impression of robustness	1. Are there unpublished data included in the third-party data set or meta-analysis that were gained without independent verification? 2. If so, how does the inclusion or exclusion of trusted data impact conclusions from the evidence base of this drug?
There is no evidence of competition bias (McGauran 2010)	When there is no evidence that any type of reporting bias is related to market competition, leading to a better positioning of the drug	Can lead to wrong conclusions because what you see may be due to market pressures	1. Do the types of bias detected (outcome emphasis, time lag. etc) favour NIs versus other drugs or interventions in particular ways? 2. Do they present a picture or tell a story which is different from all the evidence and position the NI favourably or the competitor unfavourably? 3. How does competition bias impact conclusions from the evidence base of this drug?
There is no evidence of language bias (Higgins 2011)	When there is no evidence that reporting is associated with language of target audience	Can lead to wrong conclusions because what you see may be due to the type of market being targeted	1. Is there evidence of presentation of unpublished (e.g. slide shows, product inserts) or published evidence in a particular language? 2. If so does the text in the source language differ from destination language? 3. If so, how does language bias impact conclusions from the evidence base of this drug?
There is no evidence of differences in methodological quality (McGauran 2010)	When there is no evidence of difference on methodological quality by source and outcome	Can lead to wrong conclusions because methodological quality affects estimates of effect, so if quality is not in fact equivalent, then differences ascribed	1. Is there difference in methodological quality between published and unpublished data? 2. How do differences in methodological quality impact

Table 2. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries, and published trials for the following outcomes: harms, complications, and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

		to drug performance may be false	conclusions from the evidence base of this drug?
There is no evidence of differences in sample size bias (McGauran 2010)	When there is no evidence of the presence of differences in sample in association with size and direction of results	Same potential impact as methodological quality, but with respect to sample size	1. Are there significant differences in sample sizes between published and unpublished material? 2. If so, do these impact on conclusions drawn from the evidence base?
There is no evidence of multicentre status bias (McGauran 2010)	When there is no evidence that there the presence of many or few centres is associated with size and direction of results	Can lead to wrong conclusions because what you see may be due to selection of centres and may not be generalisable	1. Are the methods used different from centre to centre? 2. If so, how do different methods impact conclusions from the evidence base of this drug?
There is no evidence of citation bias	When there is no evidence that citation of a selected study is associated with size and direction of results	Pressure is placed on authors of reports of study to provide an unbalanced interpretation or perspective by selecting citations or misreporting their content	1. Are the references in the published studies comprehensive? 2. Do they refer to unpublished material? 3. If so, how do the inclusion or exclusion of cited unpublished material impact conclusions from the evidence base of this drug?
There is no association between affiliation of authors and positive research conclusions (McGauran 2010)	When there is no evidence that differences in affiliation/ employer of authors may be associated with differences size and direction of results or conclusions drawn	This form of bias is particularly dangerous when readers' understanding or policy are based solely on the abstracts or conclusions of studies	Are there differences in study conclusions associated with affiliation of authors?
There is no evidence of publication constraints (McGauran 2010)	When there is no evidence that obstacles to publication are associated with size and direction of results	What you see has been filtered on the basis of its results	1. If unpublished studies exist, why were they not published? 2. Were data presented to regulators not published? If so, why?
There is no evidence of study design bias	When there is no evidence that there may be differences in design to emphasise size and direction of selected results	Can be misleading as design affects results and generalisability and the choice of design is influenced by considerations other than study objective and ethics	1. Is there any relationship between study design and study conclusions? 2. If so, how does the relationship impact conclusions from the evidence base of this drug?

on-t: on time frame
off-t: off time frame

IPR: intellectual property rights

APPENDICES

Appendix 1. Example of contents of CSR (from page 1 of CSR WV15670)

Final study report modules

This report consists of 5 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 EFFICAY 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

Appendix 2. Compliharms: events alternatively recorded as complications or harms

Roche Clinical Study Report of oseltamivir treatment trial: "The following symptoms, signs and common sequelae associated with influenza were excluded from specific adverse event reporting if they occurred during the period of drug treatment provided their appearance was in conjunction with one or more other influenza-related symptoms. The recrudescence of single discrete signs/symptoms associated with influenza syndrome were recorded as adverse events."
[Event by body system]
Respiratory
Cough
Pneumonia
Bronchitis/tracheitis
Sinusitis
Dyspnoea/difficulty breathing
Cardiovascular
Tachycardia
Eyes, ears, nose and throat
Sore throat
Nasal obstruction
Earache
Otitis
Coryza
Conjunctivitis
Central nervous system
Headache
Fatigue
Musculo-skeletal
Myalgia
Other
Fever
Rigor
Malaise/asthenia
Chills
Source: "Appendix 1. Events Associated with Influenza Syndrome". Roche Clinical Study Report No. W-144117, Protocol WV15707, Module I-43
A 1999 FDA medical review of oseltamivir: "As symptoms and common sequelae of influenza were collected as endpoint data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table [above] lists events associated with influenza syndrome which were excluded from adverse event reporting. … In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness). Comment: As the applicant [Hoffman-La Roche] stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness."
Emphasis in the original. Oseltamivir Medical Review. US FDA Center for Drug Evaluation and Research, Application No. 021087, 25 October 1999, page 15. www.accessdata.fda.gov/drugsatfda˙docs/nda/99/21087˙Tamiflu˙medr˙P1.pdf

Appendix 3. Modified CONSORT reconstruction template for unpublished clinical study reports

Title and drug name **Include source documents used:**		
Modified consort extraction template http://www.consort-statement.org/		
Introduction consort number		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Insert text:		
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Insert text:		
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Insert text:		
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Insert text:		
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Insert text:		
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines

(*Continued*)

Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Insert text:		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Insert text:		
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Insert text:		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

(*Continued*)

Insert text:		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Insert text:		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Insert text:		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Insert text:		
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
Insert text:		
First author Date of completion Conflicts of interest Second author check Date of check Conflicts of interest		

FEEDBACK

From Michael Power, Sowerby Centre for Health Informatics at Newcastle, 15 December 2010

Summary

From: Michael Power <michael.power@schin.co.uk>
Date: 15 December 2010 18:51
Subject: Neuraminidase inhibitors for influenza - HTA project
To: "cdelmar@bond.edu.au" <cdelmar@bond.edu.au>, "jefferson.tom@gmail.com" <jefferson.tom@gmail.com>, Carl Heneghan <carl.heneghan@dphpc.ox.ac.uk>

Hi
I picked up Carl's Twitter request for comments on your draft protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data". So, here are my two comments on the content.

The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials. It would be longer but clearer if you could call it "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".

The section "How the intervention might work" could be reorganized along the lines of:
0) Metabolism: Oseltamivir phosphate (OP), Tamiflu, is the pro-drug of oseltamivircarboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE).
1) Reducing the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006).
2) Inhibiting neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005).
3) Central depression by OT (Hama 2008) may cause hypothermia (Ono 2008).
4) Inhibition by NIs of human sialidase may cause abnormal behaviour (Li 2007).
You have obviously put a huge amount of work and expertise into developing the protocol, and have an even bigger task ahead to complete the review. Congratulations for taking this on.

Best wishes
Michael

Reply

Thanks for the constructive comments.

1. We have re-titled the Protocol to address this concern (and that of feedback from GSK, see below);
2. We have re-examined the "How the intervention might work" section, but made only small adjustments in the interest of keeping this section short;
3. We are not sure what problems you might have had printing the pdf file, and hope they are resolved with this new version.

Contributors

Chris Del Mar

from Juan C. Vergara, Intensive Care, Hospital Cruces, 48901 Barakaldo.Spain, 24 February 2011

Summary

From: JUAN CARLOS VERGARA SERRANO <JUANCARLOS.VERGARASERRANO@osakidetza.net>
Date: 24 February 2011 12:48
Subject: Oseltamivir
To: jefferson.tom@gmail.com

I've read your Intervention Protocol: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data. And may be you can be interested in this letter I wrote to de BMJ: http://www.bmj.com/content/340/bmj.c789.extract/reply
1. Early use of Oseltamivir does not reduce swine flu mortality, Juan C. Vergara, MD. Intensive Care Unit, Hospital Cruces. 48901 Barakaldo. Spain

As you say, in July the National Pandemic Flu Service started providing oseltamivir to anybody who telephoned with a plausible set of symptoms. From 23rd July to 1st December, the National Pandemic Flu Service (NPFS) in the UK, has provided more than one million courses of antiviral medication. By that time the Spanish Health Secretary General, José Martínez Olmos, at the Congress of Deputies, announced that only 6.000 patients (most of them hospitalized) had received Oseltamivir in Spain. At the end of January there have been 411 deaths reported due to pandemic (H1N1) 2009 in the UK, and about 300 in Spain. That means 6.7 and 6.5 deaths per million, respectively. These data create serious doubts about the real utility of early use of Oseltamivir in preventing deaths from Influenza A H1N1.
http://www.nhsdirect.nhs.uk/article.aspx?name=SbSwineflu
http://www.congreso.es/public˙oficiales/L9/CONG/DS/CO/CO˙411.PDF

Competing interests: None declared

Yours sincerely;
J. C. Vergara

Reply

Thank you for your interest.

Contributors

Chris Del Mar

From Dr Helen Steel, GSK, UK, 30 March 2011

Summary

GSK comments on Cochrane Collaboration protocol: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data

General:

- The term **'unpublished data'** is used extensively in the protocol. However, it does not appear to be clearly defined either in the protocol or in Jefferson's comment in the 15 Jan 2011 edition of the BMJ. Additionally, the term **'unpublished data'** is misleading. It appears the Cochrane Group use this term interchangeably with Clinical Study Reports, regardless of whether a primary manuscript is available for a given study. We suggest this is clarified or preferably replaced, especially since the term appears extensively in the protocol including the title. Readers are likely to use the terms 'unpublished data' and 'unpublished trials' (trials for

which no primary publication appears in the scientific press) interchangeably. A suggested replacement is 'Clinical Study Reports' since this term is not easily misinterpreted and is clearly defined in Jefferson's BMJ comment.

- The 'scope of clinical trial data' are defined in Jefferson's BMJ 15 Jan 2011 comment, as mentioned above (i.e. definitions for CSR, raw data, unpublished trial, published trial, regulatory data). It would seem important that these and any other definitions introduced in the protocol are included in the protocol.

Description of Intervention

- This section incorrectly describes Relenza as 'nebulized zanamivir'. Relenza is formulated in Rotadisks containing foil blisters with a powder mixture of zanamivir and lactose. Relenza is administered by oral inhalation using a breath-activated device called the Diskhaler. Earlier clinical studies explored several methods of administration, including nebulized and intranasal routes, but marketing approval in nearly all countries is currently available only for oral inhalation via Rotadisk/Diskhaler.

Types of Studies

- To meet the objective of providing a comprehensive review of neuraminidase inhibitors in preventing and treating influenza, it would seem appropriate that clinical trials from all sources (including sponsors other than industry) be included in this meta-analysis. Please clarify if this is your intent.

Outcome Measures

More details should be provided on the outcome measures section in the final protocol.

- For example, broad outcome measures are stated in the protocol, but specific endpoints are not provided. The primary and secondary endpoints of the meta-analysis should be clearly defined in the final protocol.

  - e.g.1. A stated primary outcome in the treatment studies is 'symptom relief'. Does this refer to 'the time to alleviation of symptoms' or 'reduction in symptom score' or another endpoint? Time to alleviation of clinically significant symptoms was the primary endpoint used in the majority of GSK treatment studies.

  - e.g.2. Another stated primary outcome is 'Harms'. Please provide the specific endpoints. Will this refer to 'incidence of most common AEs' or 'incidence of common SAEs', 'incidence of complications' or another endpoint? It is not clear if 'harms' are the same as 'compliharms'. It is not clear what specific events will comprise compliharms.

- Prophylaxis studies: Several types of prophylaxis studies were conducted by GSK: household prophylaxis (post-exposure prophylaxis), community prophylaxis and outbreak control in nursing homes, and as such the designs and/or endpoints are different. It is possible to measure 'prevention of onset of influenza in contacts' in these studies, but not 'reduction in viral spread from index cases' in the majority of prophylaxis studies.

- Hospitalizations: As studies were generally conducted in the setting of acute uncomplicated influenza, limited hospitalization data were collected, and are available only for some studies.

- Extracting compliharms: There is a statement that 'AEs are reported for all participants while complications are only reported for infected subjects'. This statement is not accurate for GSK trials. AEs are reported for all study participants. However, AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness. Without knowing the specific safety endpoints, it is unclear whether this will affect the outcome of some of the harms analyses.

Data collection and analysis:

- The protocol indicates that CSRs will be requested (minus participant identification). In fact many documents for each study will need to be redacted not just to remove participant identification, but any personally identifiable information including author and investigator identification.

- Missing Data. The protocol states *"At the participant level (i.e. within a trial) we will not make any assumptions about missing data."* This is not possible, because an analysis of data that is collected in a trial can only be done in the context of assumptions about potential mechanisms that led to data being missing (e.g., missing completely at random, or missing at random).

- Meta-analysis Method. Little detail is given in the protocol. The protocol states that *"Whether or not heterogeneity is detected, we will perform a random effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety)."* There are several different Random Effects methods available (Bayesian or frequentist, DerSimonian & Laird or Maximum-likelihood or REML), and different approaches to handling rare events (various "corrections" to include trials with zero counts). Furthermore, would random-effects methods also used to compare the continuous outcomes?

- Fixed-effects Model. The protocol also states that fixed-effects models will be used in a sensitivity analysis. No details are given with regard to which fixed-effects models will be used. There are several fixed-effects models available including Inverse Variance, Mantel-Haenszel, and Peto's method. The appropriate method used should also depend on the outcome measures (dichotomous vs. continuous; relative vs. absolute). The approach and choice of models for sparse data and rare events should be provided. Furthermore, various methods in the framework of fixed-effects model may be explored to evaluate the robustness of the results.

- Hazard Ratio. The protocol states *"We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) to enable meta-analysis of time to event outcomes."* Although hazard ratio (HR) is a standard analysis and widely recommended approach for time-to-event data in clinical trials, the HR analysis may not be suitable for the Relenza studies with relatively short follow up time because the assumption of proportional hazards required for the proportional hazards model may not hold. GSK did not follow this approach for the original analysis due to the concern stated above. Further the clinical and regulatory interest centred on differences in the time to alleviation not in the relative hazard between treatments. The above issues would be best addressed by using subject level rather than summary data, which GSK have offered to provide to the Cochrane Group.

- Analysis Populations. The protocol does not specify which populations will be used for the various analyses, for example, intent-to-treat or influenza positive or other. We believe that Influenza Positive population is appropriate, especially for the efficacy analysis using time to alleviation of influenza symptom as a primary endpoint consistent with the prescribing information for Relenza.

- Study Duration. No details are given in the protocol with regard to how studies with different follow up times will be handled.

- Trials with no Events. No details are given in the protocol with regard to how to deal with trials in which there are no events (such as death). By excluding studies with no events will make the event appear more common than it actually is. There are various techniques: Bayesian approach, continuity correction, combining similar trials to avoid having any components of the analysis that have no events.

- Sensitivity Analyses. Sensitivity analyses using different outcome measures, statistical models and/or continuity correction factors to assess the robustness of the results are strongly encouraged.

Reply

General:

- **'unpublished data'**. We agree that this term is confusing, and are attracted to the proposal of using 'clinical study reports' instead.
- We have attempted to ensure all terms are clear.

Description of Intervention

- Description of zanamivir (Relenza): we have corrected 'nebulized zanamivir' to 'powder inhalation'.

Types of Studies

- Yes, we intend to comprehensively review clinical trials from all sources (including sponsors other than industry). This intent is clear from the subsection " ***Electronic Searching*** " under the "**Search methods for identification of studies**" Section.

Outcome Measures

- Our specified outcomes are those of interest to patients, and their clinicians and policy-makers. They are therefore likely to be broader than the more specific endpoints selected by trialists. The purpose of Cochrane Reviews are usually to set clinically relevant review questions, and search the literature (or other sources) for answers to them. Sometimes answers to some questions are not available, and this is also documented. Where possible we report outcomes as pre-specified in the trial protocols, or as pre-specified in the review protocol, or otherwise reported as a post-hoc analysis.

    - e.g.1. 'symptom relief' may refer to 'the time to alleviation of symptoms' or 'reduction in symptom score', or any other endpoint (including 'area under the curve of symptom score and time').

    - e.g.2. 'Harms' include common adverse events (AEs) as well as serious AEs. We agree about the confusion of harms and complications, and have tried to capture the totality of these with the neologism 'compliharms' to avoid classification errors between their different labellings.

- Prophylaxis studies: We understand that it is possible to measure 'prevention of onset of influenza in contacts' in some GSK studies, but not 'reduction in viral spread from index cases' in others.

- Hospitalisations: We understand that hospitalisation data may only be available for some studies. However patient hospitalisation is usually classified as a serious adverse event therefore we expect to identify hospitalisations (not reported separately) in that way.

- Extracting compliharms: Your statement that 'AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness' underlies the complexity of analysing AEs and complications (our 'compliharms'). We have noted in the protocol that the limitation of complications only reported for the infected patients is relevant to the Roche trials only.

Data collection and analysis:

- We are interested that not only subject identification would be required to be removed from any documents of CSRs, but also information personally identifying authors and investigators. We wonder why.

- Missing Data. We have removed this statement.

- Meta-analysis Method. DerSimonian & Laird method will be used. Note that in the case of zero cells (e.g. no events in one group) the RevMan software (which we will use for the analysis) automatically adds 0.5 to each cell of the 2×2 table for any such study. There are no continuous outcomes specified in this review.

- Fixed-effects Model. Mantel-Haenszel method will be used except in the case of sparse data, in which case Peto's method will be used (as recommended in the Cochrane handbook).

- Hazard Ratio. We note the concerns with this outcome hence we will also consider analysis of this outcome as a continuous outcome noting that the data is likely to be skewed. We will use the inverse-variance random-effects method for this analysis.

- Analysis Populations. All analysis will be using the intent-to-treat population as this is the most methodologically rigorous and clinically relevant.

- Study Duration. We have specified in the protocol, where appropriate, that we will report outcomes for the on-treatment and off treatment time periods. If data is not available in the CSR for any time period of the study then we will write to the relevant manufacturer to request the missing data.

- Trials with no Events. As stated above the RevMan software automatically adds 0.5 to each cell of the 2×2 table for any such study.

- Sensitivity Analyses. We note this point and agree. Where appropriate realistic sensitivity analyses will be conducted.

Contributors

Chris Del Mar

WHAT'S NEW

Date	Event	Description
4 May 2011	Feedback has been incorporated	Feedback from three contributors has been added to the protocol

HISTORY

Protocol first published: Issue 1, 2011

CONTRIBUTIONS OF AUTHORS

All authors (except RH) were authors of the separate relevant Cochrane Reviews. The protocol was written by TJ, PD and CDM. All authors contributed to the writing of this protocol and devised the approach strategies to the data sources. CH provided logistical support.

For this review all authors will reconstruct clinical trials using the CONSORT TEMPLATE, TJ will review regulatory material, TJ, MJ, CH, and CDM will apply inclusion criteria. In Stage 2 all review authors will reappraise and extract data while CDM will supervise the process and arbitrate when necessary. MJ and CDM will check and transform data and supervise the revised meta-analysis. RH will extract harms data in pair with MJ. TJ, CDM, MT and PD will edit the text and all authors will contribute to the final draft.

DECLARATIONS OF INTEREST

All review authors have applied for and received competitive research grants. All review authors are co-recipients of a NIHR grant to carry out this review. In addition:-

Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, none of which are on NIs. He is occasionally interviewed by market research companies for anonymous interviews about Phase 1 0r 2 products unrelated to NIs.

Chris Del Mar provided expert advice to GlaxoSmithKline about vaccination against acute otitis media in 2008-2009. He receives royalties from books published through Blackwells BMJ Books and Elsevier.

Chris Del Mar and Tom Jefferson are currently updating their Cochrane Review on physical interventions to prevent the spread of ARIs (Jefferson 2010b) with WHO funds.

Rokuro Hama has written books:

1. A book published in January 2008: "Tamiflu: harmful as feared". Kin-yobi Publishing Co: royalties were split between his institution and the Tamiflu-sufferers group 7%-1%.

2. A book published in November 2008: "In order to escape from drug-induced encephalopathy". NPOJIP(Kusuri-no-Check), royalties to his institution.

He provided scientific opinions on eleven adverse reaction cases related to oseltamivir following application by their families for adverse reaction compensation. He has provided expert testimony:

1. 11 adverse reaction cases related to oseltamivir where applications were made by their families for adverse reaction relief by PMDA (Pharmaceuticals and Medical Devices Agency). This is reported in: IJRSM 2008:20:5-36. Two cases were paid in May 2005 and others not.

2. AstraZeneca and Japanese Minister of Health Labor and Welfare. Hama was an expert witness on the adverse reaction of (death from) gefitinib lawsuit, arguing that gefitinib's lung toxicity was known before approval in Japan as shown in "Gefitinib story": http://npojip.org/english/The-gefitinib-story.pdf and in other articles: http://npojip.org/. Paid by plaintiffs lawyers.

Mark Jones and **Peter Doshi** have no conflicts of interest to declare.

Matthew Thompson receives payment for running educational courses into the University of Oxford and University of Oxford ISIS consulting services for external teaching and training.

Carl Heneghan receives payment for running educational courses into the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series Blackwells BMJ Books).