

Appendix 1: Search methods for identification of clinical study reports of zanamivir [posted as supplied by author]

Searches of the electronic databases

Although this review focuses on the primary data sources of manufacturers, to check that there were no published randomised controlled trials (RCTs) from non-manufacturer sources, we ran electronic searches in the following databases:

the Cochrane Central Register of Controlled Trials (CENTRAL, part of *The Cochrane Library*, www.thecochranelibrary.com) 2013, Issue 6 limited to year published 2010-2013 (20 search results);

Medline (January 2011 to July week 2, 2013) (56 search results) and Medline (Ovid) from 01 January 2011 to July week 2, 2013 (56 search results);

Embase (January 2011 to July 2013) (90 search results) and Embase.com from 01 January 2011 to July 2013 (90 search results);

PubMed (NOT MEDLINE) no date limit (21 records) PUBMED was searched to identify publisher submitted records that will never be indexed in Medline and the most recently added records not yet indexed in Medline.

To identify reviews that may possibly have referenced further trials we searched:

- the Database of Reviews of Effect (DARE) 2013 Issue 2 of 4 April (4 search results);

- the NHS Economic Evaluation Database (NHSEED) Issue 2 of 4 April 2013, (2 search results) both resources are part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 22 July 2013).

- the Health Economic Evaluations Database (HEED) (searched 22 July 2013) (3 search results).

Previously we had searched the Cochrane Central Register of Controlled Trials (CENTRAL) (eight search results); MEDLINE (Ovid) from 1 May 2009 to 12 April 2011 (31 search results); EMBASE from 1 January 2010 to 12 April 2011 (54 search results); DARE (five search results) and NHSEED (five search results). CENTRAL, DARE and NHSEED are part of *The Cochrane Library*, www.thecochranelibrary.com (Issue 2, 2011, accessed 1 June 2011). All search results were loaded to an electronic library (*EndNote*).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We adapted the search strategy for EMBASE. We imposed no publication or language restrictions.

MEDLINE (Ovid)

- 1 Influenza, Human/ (24449)
- 2 exp Influenzavirus A/ (20342)
- 3 exp Influenzavirus B/ (2486)
- 4 (influenza* or flu).tw. (65501)
- 5 or/1-4 (70185)
- 6 Oseltamivir/ (1076)

7 Zanamivir/ (541)
8 neuraminidase inhibitor*.tw. (699)
9 (oseltamivir or zanamivir or tamiflu or relenza or peramivir or gs4071).tw,nm. (1664)
10 or/6-9 (1925)
11 5 and 10 (1769)

EMBASE.com

17 #13 AND #16 285 25 Jan 2011
16 #14 OR #15 833616 25 Jan 2011
15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 794617 25 Jan 2011
14 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 235493 25 Jan 2011
13 #4 AND #12 4283 24 Jan 2011
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 5170 24 Jan 2011
11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:ab,ti OR gs4071:ab,ti AND [embase]/lim1806 24 Jan 2011
10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti AND [embase]/lim 87 24 Jan 2011
9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti AND [embase]/lim 829 24 Jan 2011
8 'sialidase inhibitor'/exp AND [embase]/lim 5028 24 Jan 2011
7 'peramivir'/de AND [embase]/lim 322 24 Jan 2011
6 'zanamivir'/de AND [embase]/lim 2544 24 Jan 2011
5 'oseltamivir'/de AND [embase]/lim 3945 24 Jan 2011
4 #1 OR #2 OR #3 65548 24 Jan 2011
3 influenza*:ab,ti OR flu:ab,ti AND [embase]/lim 56510 24 Jan 2011
2 'influenza virus a'/exp OR 'influenza virus b'/de AND [embase]/lim 14985 24 Jan 2011
1 'influenza'/exp AND [embase]/lim 26330 24 Jan 2011

Searches for clinical study reports

Searching an unpublished and hitherto unseen data set requires constructing a reasonably accurate list of all studies of the drug in question. The obvious source of such information would be trial registries but most trials of both NIs were carried out before inception or wide acceptance of centralised registries. As single, authoritative, up-to-date and complete lists of all clinical trials conducted on humans using a given drug are rarely available in the public domain, there was no alternative to constructing our own. We decided to do so by using multiple, cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including 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](#)), such as www.ClinicalTrials.gov and www.roche-trials.com. Regulatory documents also aided the identification of unknown trials (see also [Searching other resources](#)). Finally, we also conducted traditional database searches ([Appendix 3](#)) and searches of grey literature to identify previously unknown trials.

To ensure the list did not include duplicate entries, we assigned 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 clinical study reports can be different from publications arising

from the same clinical trial). Nor are any other details connected to publications 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 cited in this review are manufacturer-funded (with corresponding manufacturer protocol IDs) and to simplify recognition and terminology we have used the manufacturer protocol ID as our Unique Trial ID.

A list is only helpful so long as it has sufficient details to enable us to decide whether it meets our inclusion criteria. For each Unique Trial ID, we gathered the following details.

1. Unique Trial ID
2. Other IDs
3. Phase of study
4. Sponsor
5. Short description
6. Official trial title
7. First authors (name and email)
8. Type of trial
9. Comparator
10. Outcomes assessed
11. Date of trial
12. Study period (days)
13. Population
14. Number of participants planned
15. Number of participants enrolled
16. Number of participants completing
17. Trial status (for example, completed, ongoing or early termination)
18. Publication status (a citation or understanding of why it was not published)
19. How identified (to record how the trial was discovered)
20. Notes

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check accuracy and completeness of our list. Roche, GSK and BioCryst all did so, and in doing so we learned of hitherto unknown trials.

Occasionally, the existence of other hitherto unknown trials was detected weeks and months after we thought we had a 'complete' list. We feel this is inevitable given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports. We engaged in prolonged correspondence with both manufacturers and requested a series of regulatory documents under FOI law from both the FDA and EMA.

Searches for Regulatory information

We searched the following sources.

1. The FDA
2. The EMEA
3. Roche
4. Japanese regulator (PMDA) SBA

We conducted a search of the FDA regulatory documentation of the New Drug Applications (NDA) and supplementary New Drug Applications (sNDA) of both drugs ([FDA 2011b](#)). The FDA NDA

documentation includes medical, statistical, microbiological and other reviews, product labels, reports of site inspections, meetings with manufacturers and records of the decision-making leading to registration and post-marketing requirements. We also searched 'Warning Letters' dispatched by the FDA ([FDA 2011c](#)).

To organise receipt of FDA materials, we created a Table of Contents (TOC) listing all the regulatory and pharmaceuticals documents accessible to us. The TOC's function was that of an index, searchable quick reference guide, and research tool to enable us to carry out quantitative (e.g. citation density analysis) and qualitative analyses (e.g. theme summaries) of the content. We also needed a rapid aide memoir with brief summaries of the evidence contained in each regulatory document listed in the TOC. We called this aide memoir the TOCE (Table of Contents-Evidence). As the TOCE contains copious working personal notes aimed to understand the regulatory narrative, we have not reproduced it here, but its content is woven into the narrative of this review.

Due to the length and format of regulatory documents, we realised in building the TOC that there was a need to formalise the search and identification methods of trials referenced in the FDA documentation. We concentrated on where each trial is mentioned in the documentation by its pharmaceutical code. So, for example if trial [WV15670](#) is mentioned 60 times by that code in a particular file, then the TOC will report the page numbers in which it is cited, which could be any number up to 60. The unit of search was the file, as a FDA PDF file can contain many different types of documents scanned into the same file. TOC and TOCE are among the tools we specifically constructed for the review ([Appendix 1](#)).

We wanted to validate our new methods, therefore we compared the yield of Optical Character Recognition (OCR) searching and hand searching of the PDF files of the FDA regulatory material using the same trial ID as a working example.