Appendix 2: Searches for Regulatory information [posted as supplied by author]

We searched the following sources.

1. The FDA
2. The EMEA
3. 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.

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

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 NAIA2005 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 (see below).

Glossary of terms used in this review

Public health drugs: Drugs in which considerable quantities of public money has been invested and/or are on the WHO essential drugs list.

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

Compliharm: Term describing events defined as either complications or harms according to ambiguous criteria that appeared to include time of analysis (with times either unspecified or inconsistent among trials) and whether participants were infected (by influenza) or not.

Time lock: Date (12th April 2011) after which no documentation would be reviewed in this iteration of the review. A cutoff was made necessary by the sheer scale of our data holdings. We were initially

funded to review the full clinical study reports of the 10 treatment trials included in the Kaiser et el paper. We were able to access the 10 Modules 1 and regulatory comments (approximately 6000 pages in total). As the funder-stipulated deadline to producing our review progressively shortened and our understanding of the issues evolved we received notification that while the balance of the ten study reports were unlikely to be accessible by our deadline, we would receive substantial quantities of regulatory documents from the EMA in four tranches. When we held our second face to face meeting in April 2011 we had just received our first tranche of clinical study reports consisting of just over 10 thousand pages, bring our total holdings to 16 thousand pages. We decided that we did not have the resources to review any further documentation within our current funding and imposed a data time lock. Any documentation received after this date would be reviewed if and when we had more resources. At the time of writing we are being granted an extension to our funding and plan to review the balance of documents (a further 14000 pages) in the next 18 months. The process is similar to that adopted in our 2009 review.

TOC: Table of content of regulatory reviews and comments on industry submissions. Our TOC indicates which trial is cited in which document in which page how many times.

TOCE: Annotated version of the TOC. Comments and annotation are preliminary and form the basis for the weaving of the important aspects into the review narrative.

Trial ID: Means of identifying a trial usually made up of letters and numbers (NAIA2005). At times the ID bears a letter suffix indicating the last version of the protocol followed in the trial (e.g. WV 15799H, i.e. trial carried out following amendment H).

Regulatory information: Term comprising clinical study reports (data) and regulatory comments and reviews.

FOI: Freedom of Information. Enshrined by law in the US and EMA policy in Europe. FOI requests in this review have been a means of access to clinical study reports and regulatory comments (regulatory information).

CONSORT-based extraction: Extraction, synthesis and appraisal method used in this review for data from clinical study reports. Reconstructions were done by pairs of review authors and assessed in the authors' plenary session to decide whether included trials could proceed to stage 2 of the analysis. The structure of the reconstruction follows that of the CONSORT statement.

Protocol: Document reporting the trial's planned design and conduct, with amendments (when relevant). Confusingly also used in submissions and regulatory documents as synonymous with study.

IPD (Individual patient data): Anonymised individual data listings of characteristics and results which form the basis for the synthetic analyses in clinical study reports.

Trial programme: Series of trials designed and carried out to achieve registration or to answer specific questions. Usually programmes of the same drug or intervention focus on the same indication or the same study population.

Reporting Analysis Plan (RAP): Plan of analysis usually linked to trial protocol explaining what and how the authors intend to analyse.

Japanese Summary Basis for Approval (of a drug) (JSBA): Summary of the application dossiers included as one of the documents prepared and attached by the sponsoring pharmaceutical company. These are submitted to the regulatory body for approval of a new drug.