PROTOCOL: Data on harms in contemporary clinical study reports submitted to the European Medicines Agency compared to clinicaltrials.gov and publications -an example from the field of oncology

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Background

Systematic reviews of randomised trials have been considered the gold standard for evaluating the effectiveness and harms of interventions for decades(1). In 1992 the first Cochrane Centre was established in Oxford(2) and since then the Cochrane Collaboration has aimed "*To produce high-quality, relevant, up-to-date systematic reviews and other synthesized research evidence to inform health decision making."(3)*

Since the very beginning of the evidence based medicine movement researchers have, however, drawn attention to problems related to relying on publications in systematic reviews as positive studies are more likely to be published than negative ones(4, 5) and studies have shown how publication bias have distorted the evidence-base.(6, 7) Additionally, even studies that are published may be unreliable due to outcome switching and selective reporting.(7-9)

In 2017 a study found that out of 203 systematic reviews 36% described no attempt to search for unpublished data and only 33% included an assessment of publication bias.Of the 64% of trials that searched for unpublished data 89% found unpublished data.(10)

One potential source of unpublished data are clinical study reports (CSRs) – extensive reports prepared by pharmaceutical companies that are submitted to regulatory authorities as a part of an application for marketing authorisation or extension of indication. The content and structure of CSRs is outlined in a guideline from the International Conference on Harmonisations.(11)

Relatively few systematic reviews have used CSRs as their main source of data, but in 2012 a Cochrane Review was published examining the use of neuraminidase inhibitors for influenza. The review considered clinical study reports the main unit of analysis and found, amongst other things, that conclusions from previous reviews regarding prevention of complications did not seem to be supported.(12)

Access to clinical study reports has historically been difficult to obtain and a request for access to CSRs made by researchers at the Nordic Cochrane Centre to the European Medicines Agency (EMA) in 2007 was initially denied because they came under the exception of commercial interests. A complaint was submitted to the European Ombudsman and in 2010, after a lengthy process, the EMA followed the recommendation from the Ombudsman to release the data.(13)

This led to a change in the EMAs policy on access to unpublished data and in 2010 the EMA published their new policy 0043 outlining that citizens of the European Union should get access to unpublished clinical data. Later policy 0070 was added, which describes making clinical study reports and other clinical information available from the EMA website as soon as an application for marketing authorisation or extension of indication is approved.(14)

Thus clinical study reports are becoming more and more available and might help solve some of the problems related to relying on published data. It is, however, unclear exactly when CSRs should be used in systematic reviews and the size of the documents might make it unfeasible to always use them.(15)

While several studies have compared reporting of harms in CSRs and other sources(16-19), we are not aware of any study that has examined the reporting of harms in relatively new CSRs released

under policy 0070 and compared the reporting to that in clinicaltrials.gov and publications in biomedical journals. We therefore wish to do so, using the field of oncology as an example.

Aims and objectives

We want to compare both quality and level of detail of reporting of harms across three potential sources of data for systematic reviews, namely:

1. Clinical Study Reports as submitted to the European Medicines Agency
2. Trial Records on clinicaltrials.gov
3. Publications in peer reviewed scientific journals.

Methods

Selection of trials

1) Identification of oncological active substances (drugs)

We will use the EMAs Clinical Data Website (https://clinicaldata.ema.europa.eu) which contains clinical study reports for all studies included in applications for marketing authorisations submitted to EMA between the 1st of January 2015 and the 31st of July 2018 as well as clinical study reports for all studies included in applications for extensions of indications submitted between 1st of July 2015 and the 31st of July 2018.(20)

We will extract the following information from all submissions available on the Clinical Data Website:

- Product Name
- Active Substance
- Marketing Authorisation Holder
- ATC code

For each submission, one reviewer (PC) will identify the indication for which the drug is prescribed and categorise them by therapeutic area (e.g., cardiology, dermatology, endocrinology, haematology, hepatology, infectious diseases, internal medicine, oncology, neurology). We will then focus on trials within the field of oncology. We will classifyactive substanceby using the ATC code, andselect monoclonal antibodies (L01XC) and protein kinase inhibitors (L01XE). We made this choice because all recent innovations in oncology concern these types of treatment.

2) Identification of trials available on the EMAs Clinical Data Website for the eligible active substances

Once all eligibleactive substances have been identified,we will download the CSRs and related documents from the EMA website and go through the documents in order to create a list of all trials for which CSRs are available.We will also note the clinical phase of development for all the trials.

In order to ensure that all eligible trials are found, the identification of trials will be performed in duplicate independently by two reviewers (ASP and PC) for one quarter of the eligible active substances. In case of any discrepancies during this phase, this identification phase will be performed by the two reviewers for all the eligible active substances.

3) Inclusion Criteria

We will select all phase II randomised clinical trials (RCTs), phase II/III RCTs, or phase III RCTs (two or three-arm trials) assessing any monoclonal antibodies or protein kinase inhibitors without any restrictions to the trial population. We will exclude trials that do not use a comparator different from the studied drug (e.g. trials testing different dosages without another comparator.)

The process of identifying and including trials will be visualised in a Flow Diagram.

Matching of selected trialswithtrial records in clinicaltrials.govand publications

1) Identification of corresponding trial records in clinicaltrials.gov

We will query the database (https://clinicaltrials.gov) using first the NCT number if it is mentioned in the CSRs, then the name of experimental drug - or its international non-proprietary name (INN). If we are unable to identify the corresponding trial record like this, other keywords will be used: e.g. treatment comparator and indication.

If we are not able to locate a corresponding trial record on clinicaltrials.gov, we will search the WHO International Clinical Trial Registry Platform (WHO ICTRP: apps.who.int/trialsearch/) and the European Clinical Trials Database (https:/www.clinicaltrialsregister) using the same method as described above.

2) Identification of corresponding journal publications

First, we will look at publications indexed as being related to the trial record on clinicaltrials.gov, both those listed under “publication of results” and those listed under “publications automatically indexed to this study by ClinicalTrials.gov identifier (NCT Number) “. We will include all publications that publish information about harms.

If no publications are indexed on ClinicalTrials.gov, we will search MEDLINE and EMBASE using the following information — name of experimental drug (or its INN), treatment comparator, indication — and the name of the principal investigator.

Data Extraction

For each trial, we will extract information from the CSR, the clinicaltrials.gov trial record and publications respectively. The information extracted will be entered into a common spreadsheet.

<u>Data to be extracted from clinical study reports, clinicaltrial.gov, and journal publications:</u>

We will extract the following from all the included sources of data:

- NCT number
- Name of the trial
- Number of patients randomised
- Whether a definition of safety population is provided (as a dichotomous variable (Yes/No) and quotes)
- Number of patients in safety population
- Threshold for reporting adverse events: e.g. either 10%, 5% or 0%

- Number of patients experiencing at least one adverse event
- Number of adverse events
- Number of patients experiencing at least one serious adverse event
- Number of serious adverse events
- Number of patients experiencing at least one adverse event judged to be of grade 3-5 according to the Common Terminology Criteria for Adverse Events (CTCAE)
- Number of adverse events judged to be of grade 3-5 according to the CTCAE
- Number of patients discontinuing the trial due to adverse events
- Number of deaths due to adverse events
- Whether a description of the process of determining whether a death was due to adverse events, including whether the person(s) making the judgement were blinded, is provided (as a dichotomous variable (Yes/No) and quotes)

For the CSRs, we will also note whether any parts of the CSR necessary for an adequate judgement of harms have been redacted.

For all variables concerning numbers, we will note whether a number is reported. If that is the case, we will also note the number for each arm.

The data extraction will be performed independently by two reviewers for 10% of the included trials (ASP and PC). If the reviewers agree in all cases, the remaining data extraction will be done by one reviewer (ASP)using PDF software to highlight where the data has been extracted from. Asecond reviewer (PC) will check the data extracted by the first. Any discrepancies will be solved by discussion.

Analysis

We will summarize how many variables are reported in each source of data for all trials. For each variable we will give the proportion of studies adequately reporting the variable in each source of data.

We will calculate the median (and inter-quartile range) number of variables reported for each source of data.

Where numbers are available from CSRs and other sources of data we will determine if these numbers match. If there are any discrepancies we will note whether the discrepancy favours the experimental treatment or the control treatment. For these calculations we will use the number reported in the CSR as our reference. A difference will be classified as favouring the experimental treatment if the number of events changes so that the number of events becomes relatively higher in the control arm as compared to the experimental arm.

We will visualise over findings using tables and graphs.

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