The use of clinical study reports to enhance the quality of systematic reviews: a survey of systematic review authors

**1\*Alex Hodkinson,**

**1Kristina Charlotte Dietz,**

**2Carol Lefebvre,**

**3Su Golder,**

**4Mark Jones,**

**5Peter Doshi,**

**6Carl Heneghan,**

**7Tom Jefferson,**

**8Isabelle Boutron,**

**1\*\*Lesley Stewart**

1 Centre for Reviews and Dissemination, University of York, York, YO10 5DD, UK.

\*Corresponding author: ​Research Fellow in Evidence Synthesis, Centre for Reviews and Dissemination, A/B Block, Alcuin College, University of York, York, YO10 5DD, UK; alex.hodkinson@york.ac.uk (A. Hodkinson).

\*\* Professor Lesley Stewart, Director of the Centre for Reviews and Dissemination, University of York, YO10 5DD, UK. Co-Convenor of the Cochrane IPD meta-analysis group.

2 Independent Information Consultant, Lefebvre Associates Ltd, Oxford, UK; Co-Convenor, Cochrane Information Retrieval Methods Group.

**3** Department of Health Sciences, University of York, York, YO10 5DD, UK; Co-convenor of the Cochrane Adverse Effects Methods Group.

4School of Public Health, University of Queensland, Brisbane 4006, Australia. Deputy Co-ordinating Editor of the Cochrane Acute Respiratory infections group.

5Assistant Professor, Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Maryland, U.S.A. Member of the Cochrane Acute Respiratory infections group.

6 Professor, Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, Primary Sciences Division, University of Oxford, UK. Editor for the Cochrane Collaboration's acute respiratory infections group.

7 Senior Associate Tutor, Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, Primary Sciences Division, University of Oxford, Oxford OX2 6GG, UK. Editor for the Cochrane Collaboration's acute respiratory infections group.

8 Professor of Epidemiology, METHODs team, Centre of Research in Epidemiology and Statistics Sorbonne Paris Cité, INSERM UMR 1153, University Paris Descartes, Paris, France. Co-Convenor for the Cochrane Risk of Bias Methods group.

# Abstract

**Background** Clinical study reports (CSRs) are produced for marketing authorization applications. They often contain considerably more information about, and data from, clinical trials than corresponding journal publications. Use of data from CSRs might help circumvent reporting bias, but many researchers appear to be unaware of their existence or potential value. Our survey aimed to gain insight into the level of familiarity, understanding and use of CSRs, and to raise awareness of their potential within the systematic review community. We also aimed to explore the potential barriers faced when obtaining and using CSRs in systematic reviews.

**Methods** Online survey of systematic reviewers who; (i) had requested or used CSRs, (ii) had considered but not used CSRs and (iii) had not considered using CSRs. Cochrane reviewers were contacted twice via the Cochrane monthly digest. Non-Cochrane reviewers were reached via journal and other website postings.

**Results** 160 respondents answered an open invitation and completed the questionnaire, 20/160 (13%) had previously requested or used CSRs and other regulatory documents, 7/160 (4%) had considered but not used CSRs and 133/160 (83%) had never considered this data source. Survey respondents mainly sought data from the European Medicines Agency (EMA) and/or the Food and Drug Administration (FDA). Motivation for using CSRs stemmed mainly from concerns about reporting bias 11/20 (55%), particularly outcome reporting bias 11/20 (55%) and publication bias 5/20 (25%). The barriers to using CSRs noted by all types of respondents included: current limited access to these documents (43 respondents), the time and resources needed to obtain and include these data in evidence syntheses (n=25), and lack of guidance about how to use these sources in systematic reviews (n=26).

**Conclusions** Mostrespondents (irrespective of whether they had previously used them) agreed that access to CSRs is important, and suggest that further guidance on how to use and include these data would help to promote their use in future systematic reviews. Most respondents, who received CSRs considered them to be valuable in their systematic review and/or meta-analysis.

# Introduction

The findings of clinical trials as reported in journal articles can sometimes be incomplete and misleading. There is evidence that analyses and outcomes, including both efficacy and harms may be reported selectively such that the true effects of treatments remain hidden [1-4]. Consequently, those performing systematic reviews and meta-analyses may need to take additional steps to locate, appraise and synthesize missing or inadequately reported data in order to minimize the impact of such reporting bias.

Clinical study reports (CSRs) are documents produced by pharmaceutical companies that are submitted as part of a marketing authorization application for investigational medicinal products in the EU, Japan, and the USA. They are usually written in accordance with the ‘international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use’ (ICH) guideline on the structure and content of clinical study reports (ICH E3) [6]. The purpose of the ICH guidance is to assist sponsors in developing a comprehensive trial report that is complete, well-structured and easy for regulators to review when making licensing decisions [7].

CSRs often include greater detail about trial design, conduct and analysis, more complete results and a more reliable picture of strengths and weaknesses than journal articles. Extracting data from CSRs and using these in systematic reviews and meta-analyses may therefore provide more complete information and generate more reliable effect estimates [5, 6] than using data presented in journal articles and provide a means of helping circumvent reporting bias [7, 8], particularly in relation to adverse events [9-12].

CSRs are becoming increasingly available and accessible following liberalisation of the European Medicines Agency (EMA) policy related to public access to documents it holds relating to market access applications [13]. Since then, requests to the EMA for access to CSRs [14, 15] have increased from 20 requests per month during the first 2 years to nearly double that in the following 6-month period. CSRs are now considered a valuable resource in systematic reviews [5-7, 10]. The shift towards improved transparency continued with the implementation of EMA’s Policy 0070 for publication of clinical data of medicinal products for human use [16], and other significant efforts to provide broader access to clinical trial data. These include the Yale University Open Data Access (YODA) Project [17], ClinicalStudyDataRequest.com (CSDR) [18], the Duke Clinical Research Institute (DCRI) [19], the AllTrials campaign [20] and OpenTrials.net [21]. Some of the world’s largest pharmaceutical companies including Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Lilly and Roche have committed to data sharing [22]. Because data sharing directly via companies and other various platforms are still relatively new, their existence may still be unknown to many systematic review authors, and their utility is yet largely unexplored [23].

The US Agency for Healthcare Research and Quality (AHRQ) has, amongst others, noted the value of searching for ‘regulatory documents’ as a means of addressing reporting bias [24]. The term ‘regulatory documents’ can be used to describe a number of sources of information other than CSRs, including Food and Drug Administration (FDA) approval documents on the Drugs@FDA website (e.g. medical and statistical reviewer reports), European Public Assessment Reports and any document produced by, or held by, a regulatory agency.

The current version of the Cochrane Handbook, last updated in 2011, encourages authors to search for unpublished data from pharmaceutical companies, trial registries and trial results registries [25]. It does not, however, discuss searching for or considering the use of CSRs and other regulatory documents as sources of data, which could partly explain why there have so far been few Cochrane Reviews that have sought data from open access sources[9, 26]. This will be addressed in the major revision currently in preparation.

Recognising the need to consider the potential value of CSRs and other regulatory documents as a potential source of data for Cochrane Reviews of pharmacological interventions, Cochrane funded a project (of which this survey was part) to explore the rationale for such use, and the readiness of Cochrane reviewers to engage with regulatory material. To assess readiness and raise awareness, we carried out a preliminary survey to gain insight to the level of understanding, familiarity with and views on the importance of CSRs and other regulatory documents. We also explored what has previously motivated authors to seek data from these sources, and barriers to using them in Cochrane and other systematic reviews. We then carried out a follow up survey of respondents who had considered or used regulatory data in their systematic review, to explore under what circumstances they thought it most important to seek CSRs as a data source.

# Methods

We conducted two online surveys involving authors of Cochrane and other systematic reviews using the data capture tool Qualtrics [27]. The initial survey (Appendix 1) was open between 10th June and 19th September 2016. This was split into two releases, one intended for Cochrane authors and the other for authors of systematic reviews conducted outside of Cochrane. A second (follow-up) survey (Appendix 2) was open between 21st April and 31st May 2017.

The survey design included closed and open-ended questions. Response options were discussed, drafted and refined by the team. Question types included multiple choice (Check one/Check all), free-text and comments. ‘Other (specify)’ responses were offered to capture more detailed information that could not be collected using structured multiple choice questions. Pilot testing of the survey logic and flow was performed by AH and checked by members of the research team and four independent researchers. Revisions were made where necessary.

Ethics approval for the survey was granted by the University of York Health Sciences Research Ethics and Integrity Governance Committee.

**Sample selection**

The release of the initial survey intended for Cochrane review authors was first announced in the Cochrane Digest, which was emailed to all Cochrane authors on 10th June 2016. This email was sent out again two weeks later. The release intended for authors of non-Cochrane reviews was first advertised on the University of York Centre for Reviews and Dissemination web site on the 25th June 2016 and then on the Systematic Reviews journal web site. Links to this were also shared via social media. The follow up survey was sent only to those Cochrane respondents who had previously considered or used regulatory data in their systematic review and who had agreed during the first survey to participate in the follow-up Although several authors of this manuscript have previously used data from regulatory documents, purposely none participated in either survey

**Domains of interest**

The first survey questionnaires were accessed via three separate links within the adverts corresponding to the respondent’s experience and understanding of the regulatory process aiming to capture those who had:

1. *‘Requested’* (i.e. had used data from CSRs in their review, had received data but decided not to include it or were still awaiting for data)
2. *‘Considered’* using but not requested access to CSRs
3. *‘Never considered’* the use of regulatory documentation such as CSRs

Respondents who had previously ‘requested’ CSRs or other regulatory documents were asked to explain their reasons for seeking and for using (or not using) the data; the source and type of documents obtained; and how the data were used in the review. They were also asked to describe any difficulties in using provided documents and data, along with their views on the overall importance of seeking data from these sources. Respondents that had only ‘considered’ seeking regulatory documents were asked about what sources they had considered utilising and why they had decided against it; and whether they thought this decision could have impacted on the outcome of their review. Other domains of interests captured were the respondents views on the barriers to using data from regulatory documents and what could be done to promote and support the use of such data in future systematic reviews.

The follow-up survey explored what factors might be considered most influential when deciding whether to look beyond the information presented in journal articles, and to seek data from CSRs or other regulatory documents for use in a systematic review. We drew up an initial list of criteria on which respondents were asked to comment (Table 1). Likert scales (very important, important, less important, not important and unsure) were used to grade the importance of each criterion. Respondents were also asked to identify any additional criteria that would be important when deciding whether to seek data from regulatory documents.

**Data analysis**

Descriptive statistics were used to express quantitative responses including number(s), frequencies and percentages. Verbatim responses were discussed within the team and then tabulated. As these responses were generally short and wide-ranging, the team decided that a formal thematic analysis approach was not required. Hence qualitative data were simply coded into categories by two research team members (AH, KCD).

Since the two first survey questionnaires intended for (a) Cochrane and (b) for other systematic review authors were the same, and because some respondents answered the Cochrane questionnaire based on non-Cochrane reviews and vice versa, and as there were few responses to the non-Cochrane version, we combined and analysed responses to both together. We firstly checked that there was no duplication and double counting of reviews. We obtained publications for the systematic reviews to which respondents referred (if provided by the respondents in the survey). This enabled us to confirm whether reviews were Cochrane reviews or not, and to help resolve ambiguity in free-text responses (i.e. to determine exactly how the data were used in a review). These references were also used to determine how successful data requests were and how such data were used within a review. Authors were contacted directly by email to confirm any other questions we had about their review.

# Results

A total of 160 respondents completed the first (Cochrane and non-Cochrane) surveys (Figure 1). Most respondents (93%) were either a Cochrane review author or editor, 70% worked in academia, 40% were clinicians, and 15% were involved in methods research. Of the 160 respondents, 20/160 (13%) had previously requested or used regulatory data in their review (13 in a Cochrane review and 7 in a non-Cochrane review), 7/160 (4%) had considered but not used regulatory data and 133/160 (83%) had never considered using regulatory data.

In the follow-up survey, all 20 respondents who had requested or used regulatory data in a systematic review explained the rationale for making the request, 19/20 (95%) provided information on where data were requested from, and 14/20 (70%) expressed an opinion about the type of barriers involved. All 7 respondents who considered using regulatory data but did not go on to seek it explained the rationale for doing so; 5/7 (71%) gave the primary source of the data under consideration and all responded about potential barriers. For the 133 respondents that had never considered using regulatory data, 91/133 (68%) were familiar with the regulatory process and types of documents produced, 39/133 (29%) were aware of where they might be able to access regulatory documents such as CSRs, and 61/133 (46%) believed that there are barriers to accessing and using data from these sources.

**Rationale for seeking data**

For the respondents that had requested or used regulatory data, 15/20 (75%) believed that regulatory data should be used in systematic reviews, and 5/20 (25%) said that they should be used in some cases (Appendix 3 – Table 1). Seeking regulatory data was mainly driven by concerns about reporting bias ((n=11) outcome reporting bias, (n=5) publication bias), and potential for missing data or underreporting of harms. The same concerns were raised by respondents who had considered but not sought regulatory data, with 3/7 mentioning outcome reporting bias, and 2/7 underreporting of harms.

For respondents who had never considered using regulatory data, 66/133 (50%) agreed that they should be used in some cases, 43/133 (32%) said they should definitely be used, 17/133 (13%) said they should not be used, and 7/133 (5%) said they were unsure about using regulatory data but did not provide any reasons. The stated reasons for the 17 respondents who said that regulatory data should not be used were: (n=9) because the interventions explored in their reviews were non-pharmacological, (n=5) because of lack of guidance on how to find and use these data, and (n=3) because of the time required to receive the data.

8/133 (6%) of the respondents who had never considered using regulatory documents indicated that they had a detailed understanding and 83/133 (62%) a basic understanding of the regulatory process (Appendix 3 – Table 2). However, 42/133 (32%) respondents said that they had no understanding of the regulatory process or the documentation involved. The majority said that they were aware of the ongoing debates and initiatives for improved access to clinical trial data; specifically referring to the AllTrials initiative [20], the Cochrane review of neuraminidase inhibitors (which was based entirely on regulatory data) [7] and other publications such as Ben Goldacre’s Bad Science and Bad Pharma. One respondent said that they had been involved in crafting the EMA-led public deliberations regarding the Policy 0070 in 2014, for access to clinical trial data [16].

**Source of evidence**

Figure 2 shows where data access requests were made (including the respondents who made multiple requests to different sources). In total there were 47 requests, of which 19/47 (40%) were made to regulatory agencies; 10/19 (53%) of these being to the EMA with seven of the requests successful in obtaining data, and 9/19 (47%) being to the US Food and Drug Administration (FDA) where five requests were successful. 18/47 (38%) requests were made directly to pharmaceutical companies; 8 to larger companies where six (75%) requests were successful, and nine to smaller companies where 3 (33%) requests were successful. A further request was made to the National Institute for Occupational Safety and Health in the US [28] for summary adverse events data, and another to Health Canada. Two requests were made to the data sharing websites, Clinical Study Data Request (CSDR) and YODA where each were successful in obtaining the data.

Amongst the 20 respondents who requested regulatory data (Table 2); sixteen (16/20) had obtained and used the data in their review, two (2/20) had not yet received the data and their review was ongoing at the time of completing the survey. One (1/20) respondent said they had received only baseline data and therefore did not include it in their review, and one (1/20) reported being unable to access the full data because the study was stopped early due to reports of unexpected side-effects. Clinical study reports were acquired by 12/20 (60%) of the respondents, five (5/20) obtained Medical and Statistical Reviews from the FDA, two (2/20) obtained European Public Assessment Reports (EPARs), and one (1/20) used other regulatory material including a protocol, case report forms and adverse reaction reports. Of the respondents who obtained CSRs, nine (9/12 (75%)) had used data from them to enable inclusion of unpublished trials in their meta-analyses (n=2) and to supplement published data (n=7). The other two respondents who obtained CSRs used them in a narrative synthesis; one within a NICE Single Technology Appraisal (STA).

Of the 133 respondents who had never considered accessing regulatory data, 117/133 (88%) said they were not aware (or were unsure) of where to access such material (Appendix 3 – Table 3). Sixteen (16/133 (12%)) respondents said that they were aware of at least one possible source of regulatory data. As expected, the EMA and FDA were the two sources most commonly noted, but other regulatory agencies mentioned were The Health Products Regulatory Authority of Ireland, Pharmaceuticals and Medical Devices Agency of Japan and Therapeutic Good Administration Department of Health Australia. Other sources mentioned but not considered to be specific to regulatory data, included the trial registries (ClinicalTrials.gov and the ISRCTN register). The clinical study data request sharing platform was considered by only one respondent, and pharmaceutical companies and ethics committees were also mentioned as other sources of data.

**Barriers**

Survey respondents were asked to express views on the real or perceived barriers to accessing and using regulatory data (Table 3). Over 70% of the authors that had used, requested or at least considered regulatory data, reported there to be barriers compared to 50% for respondents that had not considered the use of such data. Specifically, for those that had requested data, 14/20 (70%) identified barriers including ‘restricted and limited sharing of trials data’, and the ‘time-constraints involved [in] searching and requesting the data’, ‘the lack of experience on extracting data and [lack of] statistical guidance when including in a review’, ‘how and where to search for individual trials’ and one mentioned ‘concerns over the quality of the data compared to the journal publication’. For respondents who had only considered (but not requested) regulatory data, 6/7 (86%) indicated similar barriers. For respondents who had not considered using regulatory data, 67/133 (50%) believed there to be barriers, whilst 56/133 (42%) were unsure. The barriers expressed in this group were also similar in citing ‘cost’, ‘time and resources required’, and also ‘limited access for the peer reviewer’.

**Criteria considered important for using regulatory data**

Results of the follow-up, targeted survey designed to identify the main reasons or triggers for authors seeking and using data from regulatory documents, are shown in Figure 3. This was sent to the 21/27 (78%) first survey respondents who had agreed to participate in a follow up. Fourteen of the 21 (66%) provided a response. The following criteria were considered of most importance (i.e. ‘very important’ or ‘important’) by all respondents in deciding when it is most important to use regulatory data in a systematic review: “discrepancies between publication and registry entry”, “known errors or concerns about publications”, “concerns for a lack of published data on harms of product”, “important outcome measures (‘endpoints’) unpublished”, “safety concerns identified in post-marketing surveillance”, “high proportion of trials unpublished and/or industry funded”.

Between, 9/14 (64%) and 13/14 (93%) of respondents considered; “marketing authorization based on surrogate outcomes”, “safety or efficacy advantage over current treatments”, “product new to the market or from a new drug class”, “important drug-drug interactions”, and “monetary cost of the intervention” as being important.

Criteria deemed less important (6/14 (43%) to 9/14 (65%) of authors) included the public availability of “statistical analysis plans” and of “protocols” respectively, which were the criteria considered as least important in over 61% of authors.

Respondents expressed divided opinion about whether; “number of people using the product”, “high degree of media attention surrounding the drug” and “burden of disease” were important triggers.

Respondents suggested other ‘triggers’ for seeking and using of regulatory data as; “*the lack of clarity on published trials*”, “*when a small number of trials are available*”. It was also noted that *“regulatory data were irrelevant for non-pharmacological intervention reviews (e.g. surgical techniques, psychological interventions, and psychical therapy), and were therefore unable to use CSRs.”*

# Discussion

**Summary of findings**

In this survey, only 27/160 (17%) systematic review authors had used, requested or considered using regulatory data in their review and, 133/160 (83%) had never considered using such data. Respondents who had requested regulatory documents had mainly sought these from the EMA and the FDA. Other requests were made to individual pharmaceutical companies, but few were made to data sharing platforms. Respondents also described seeking data from the clinical investigators or authors of published trials in their responses, although these are clearly not usual sources of regulatory documents, and which may indicate a misunderstanding of the question posed as being about any ‘unpublished data’ rather than specifically being focused on regulatory documents.

Clinical study reports were acquired by 12/20 (60%) of the respondents requesting data, but other regulatory documents including Medical and Statistical Reviews from the FDA (5/20 (25%)), European Public Assessment Reports (EPARs) (2/20 (10%)), and protocols, case report forms and post-marketing adverse reaction reports were also obtained. For the respondents who obtained CSRs, 9/12 (75%) had used the data in their review, in order to include unpublished trials in their meta-analyses and to supplement published data. Two of the respondents were still waiting for the data, one respondent noted that the pharmaceutical company could not provide the data because the study for which the request was made was stopped early due to reports of unexpected side-effects, and another respondent reported that only baseline data were provided.

At least two-thirds of respondents who requested or considered utilising regulatory data, reported a number of barriers to using these data in Cochrane reviews. Identified barriers were restrictions on accessing trial data, the excessive time involved when waiting for data to be released, and the resources, costs and effort required when incorporating the data in a review.

The criteria considered to be most important in triggering decisions to seek regulatory data, include where there exists discrepancies between the publication and registry entry, known errors or concerns about publications, concerns of a lack of published data on harms, important outcome measures (‘endpoints’) that are unpublished, safety concerns identified in post-marketing surveillance, a high proportion of trials unpublished and/or industry funded, where marketing authorization was based on surrogate outcomes and when there are clear safety or efficacy advantages over the current treatments. The availability of the trial protocol and statistical analysis plan, and media attention about the drug were considered to be ‘less important’ in over 60% of respondents. The cost of the intervention, disease burden, population size and characteristics of the intervention (new to market, interactions with other drugs), were also considered to be important criteria amongst authors.

**Comparison with other research**

A previous study [9] exploring the experiences of Cochrane review authors when searching for, gaining access to, and using unpublished data, found that a large proportion of Cochrane review authors had searched for unpublished data. Over half (913/1656 (55.1%)) of those who searched for unpublished data were successful in finding it, and over 81% (651/794) who sought these data went on to use them in their review. In that study most of the unpublished data were obtained from ‘trialists or investigators’. Of 794 author requests in their study, 403/794 (51%) sought summary data (e.g. mean, standard deviation, sample size), 226/794 (29%) missing outcomes (e.g. quality of life), 163/794 (21%) individual participant data (IPD), 96/794 (12%) results of alternative analysis (e.g. intention to treat), 67/794 (8%) data on harms and 45/794 (6%) CSRs. Data from manufacturers were less frequently used in these reviews. One of the concerns outlined by the authors was that searching for unpublished data was time consuming, which aligns with the opinions expressed by respondents in our survey. Despite the perceived importance of CSRs in providing information about adverse effects, a recent study found that of 348 systematic reviews on adverse effects published in 2014, not one of the reviews had stated that they searched for or included CSRs [26].

Another study [29] provided in-depth descriptions of some of the experiences of researchers carrying out systematic reviews when searching for and gaining access to unpublished data. That work aimed to provide guidance on best practices for identifying, obtaining, and using unpublished data from a variety of sources, but did not consider regulatory documents. The results suggested that authors differed in their understanding of what was meant by *unpublished data*, including specific outcomes and methodological details. They also reported that data requests were often seen as time-consuming and that including such data was considered to be labour-intensive. There was agreement, however, by the majority of authors that searching for and considering unpublished data in systematic reviews was important for public health.

**Accessing Regulatory data**

Many researchers are still unaware of the various data sharing platforms that provide access to regulatory trial documents and datasets. This may be partly because such data sharing platforms are relatively new and evolving, and that organisational positions on access to regulatory data are developing and changing rapidly. Furthermore, the limited guidance available to systematic review authors about how to identify and access regulatory data might also explain why they are rarely used or even considered. For example, as noted above, the current version of the Cochrane Handbook does not currently discuss regulatory documents and the data that these might contain, where to find these data, or how to include them [30]. In our study, participants were asked what could be done to promote and support greater use of CSRs and other regulatory documents. Most agreed that there is a need for greater understanding about these documents and for guidance on how to search for and access such data. Some mentioned the need for statistical guidance on how to include the data in evidence synthesis, even though the type of (aggregate) data that these documents contain is no different to the type of data presented in journal articles and generally they do not need to be handled and analysed any differently. There were also concerns on how to interpret highly statistical content within the documents, e.g. efficacy and safety listings data which may require statistical/software expertise to help extract and organize the data.

**Limitations of study**

As most of the survey questions captured free-text response(s), the replies were varied and some were unclear or lacked enough detail to fully understand. However, responses were discussed by two team members (AH and KCD) who agreed upon an appropriate classification of response.

Although this survey concerned regulatory documents, and in particular CSRs, it was apparent even from the relatively low numbers who responded to this survey that some may have misunderstood the questions posed. The terms ‘regulatory data’ and ‘unpublished data’ were not defined in the survey, as we intended to leave this open to interpretation. This may explain the reasons why some authors who had used other types of data (e.g. IPD or other summary data obtained from trial authors) participated in the survey. In a number of the responses, authors had made multiple data requests for regulatory data and other data, but it was often unclear which data or document sources were actually used in their systematic review or meta-analysis. The review references provided, or obtained by contacting the authors helped to confirm some of the uncertainties that we had about how the data were used in their review.

The survey was advertised twice in the Cochrane review and methods digest, which is circulated by email to the whole Cochrane community. We do not know how many recipients of the digest read or even opened the email and consequently how many people read the invitation to opt into the survey. This might explain the low response rate (2.2%) compared with that achieved in the other survey by Schroll et al (37%). In addition, survey respondents may have been more likely to have a greater understanding of the regulatory process and documents produced, than authors who did not participate in our survey. Therefore our sample might not be representative of all authors of systematic reviews. The survey cannot be used and indeed was not intended to draw any conclusions about the proportion of reviewers accessing CSRs. Rather it aimed to gain insight into the level of familiarity with regulatory sources of data, particularly among Cochrane authors, and to get some indication of the potential level of ‘buy in’ to future encouragement to use these sources in Cochrane Reviews, and what support may be needed to facilitate this.

**Conclusions**

The results from this survey show that data from CSRs and other regulatory documents are being used in a small number of Cochrane Reviews. The survey revealed that the vast majority of respondents thought that accessing and using CSRs and other regulatory documents in systematic reviews was important, suggesting that the Cochrane community may be ready and willing to engage with this source of evidence. The time taken and resource needed to request, receive and use the data was cited as a major barrier, as was the lack of guidance on access to and use of documents produced for regulatory purposes. There is a pressing need to develop guidance to help review authors identify questions and topics where using regulatory data is likely to matter most, to help them identify those reviews which should adopt and invest in such an approach, and to help them navigate regulatory documents and incorporate data from them in Cochrane and other systematic reviews.

National laws such as the Food and Drug Administration Amendments Act (FDAAA) have gone some way to address reporting bias by requiring applicable clinical trials to post summary results for registered outcome measures and adverse events to ClinicalTrials.gov within 12 months of trial completion [31, 32]. Consulting such result registries should enable review authors to (i) identify and access results from a large number of unpublished trials and (ii) to locate additional outcomes and results that published trials have omitted to report. However, a 2012 study indicated that only around one quarter of trials comply with this requirement [33], and a more recent study found that of more than 224,000 ClinicalTrials.gov study records only 23,000 (10%) displayed adequate results information [34]. The US Agency for Healthcare Research and Quality (AHRQ) has, amongst others, noted the value of searching for regulatory documents as a means of addressing reporting bias[24]; the term ‘regulatory documents’ can be used to describe a number of sources of information other than CSRs, including Food and Drug Administration (FDA) approval documents on the Drugs@FDA website (e.g. medical and statistical reviewer reports), European Public Assessment Reports and any document produced by, or held by, a regulatory agency.

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**Contributors**

The study protocol was drafted by AH, LS and other members of this Cochrane Methods Innovation Funded (MIF) project contributed. AH created the online survey which was pilot tested by the MIF members; LS advertised the survey via Cochrane and Systematic Reviews journal homepage; AH tabulated the data and KCD checked for consistency. The data were analysed by AH, and AH, LS drafted the manuscript. AH is guarantor and takes responsibility for the integrity of the data and the accuracy of the data analysis. All other MIF authors have edited and approved the final manuscript. Referencing was organized by SG.

**Acknowledgements**

We thank CRD staff members Ruth Walker, Hollie Melton and Matthew Walton for helping with the pilot testing of surveys; Toby Lasserson, Senior Editor, Cochrane Editorial Unit, for providing a denominator for the number of active Cochrane reviews over the last 2 years.

**Funding**

This study was funded by the Cochrane Methods Innovation Fund: <http://methods.cochrane.org/methods-innovation-fund-2>. The funder had no influence on the study design, interpretation of data, or the decision to publish the results.

**Competing interests**

All authors have completed the ICMJE uniform disclosure form at

[www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for submitted work; no financial conflicts of interest.

**Ethical approval**

This study was granted ethical approval by the University of York Health Sciences Research Ethics and Integrity Governance Committee on 16th May 2016.

**Data sharing**

Anonymised datasets of survey responses and protocol are available on request from the corresponding author at alex.hodkinson@york.ac.uk

**Table 1: Important criteria when considering data from clinical study reports and/or other regulatory data**

|  |  |
| --- | --- |
| **Criteria** | **Description of criteria** |
| 1 | Monetary cost of the intervention on the healthcare budget (i.e. considering both the price of a course and the number of people in the population that are being - or will be treated) |
| 2 | Burden of disease of the indication this product is meant to treat/prevent |
| 3 | How many people are using or likely to use this product? |
| 4 | Product new to the market? |
| 5 | Product from a new drug class or has a new mechanism of action |
| 6 | Has important interactions with other drugs (e.g. drug-drug interactions) |
| 7 | High proportion of RCTs evaluating this product are industry funded |
| 8 | Prominent claims of safety and/or efficacy advantage of this product over currently available treatments |
| 9 | High degree of media attention surrounding this product |
| 10 | High proportion of trials of this product are unpublished |
| 11 | Post-marketing surveillance has identified safety concerns? |
| 12 | Important or standard outcome measures (also known as 'endpoints') have not been published |
| 13 | Concerns regarding a lack of published data on potential harms of the product |
| 14 | Marketing authorization based on surrogate outcomes (rather than clinical outcomes) |
| 15 | When protocol(s) are publicly available |
| 16 | When statistical analysis plan(s) publicly available |
| 17 | Known errors or concerns about trial publications of this product |
| 18 | Important discrepancies between the journal publication and the trial registry entry? |

**Figure captions and footnotes:**

**Figure 1: Flow diagram of combined survey responses with responses in each domain of interest**

**Figure 2: Sources of data for the respondents who requested regulatory/non-regulatory data and the success rate obtaining the data**

**Footnote for figure 2**

\*Larger companies include: GSK (n=1 request (1: successful request)), Pfizer (n=2 (2)), Eli Lilly (n=1 (1)), Bristol-Myers Squibb (n=2 (1)), Merck (n=1 (0)), Genentech (n=1 (1)).

\*\*Smaller companies include: (2) Helsinn, (2) Schering-Plough, (1) Salix Pharmaceuticals, (1) PharmaSwiss, (1) Cubist Pharmaceuticals, (1) Pharmaxis, (1) Santhera.

\*\*(1) Request was made to the US’s National Institute for Occupational Safety and Health (NIOSH) and the other to health Canada.

**Figure 3: Criteria considered most important when considering using regulatory data (n=14)**

**Table 2: Description of data obtained and how they were used in the systematic reviews**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Survey reply** | **Source of data request(s)** | **Data obtained** | **Type of regulatory data/document(s) obtained** | **Included in meta-analysis** | **Description of how data were used** |
| 1 | Author, manufacturer | Yes | CSRs | Yes | “Summary statistics provided or extracted from the extra documentation were incorporated into meta-analysis” |
| 2 | Unknown  | Yes | CSRs | Yes | “Quantitative data about side effects were included” |
| 3 | EMA, FDA  | Yes | CSRs | No | “Data were not used in meta-analyses, but rather in a narrative form instead” |
| 4 | EMA, FDA | Yes | EPARs and Medical Reviews | No | “Data was used to describe the number of studies and the number of studied drugs in results of search criteria” |
| 5 | EMA, FDA, Multiple drug companies | Yes |  FDA and EMA reports, Poster | Yes | “To add data on studies not aware of, and to add outcomes to a published study that were not itemised in the journal publication” |
| 6 | Clinical investigator, EMA, sponsor  | Noβ | No data were obtained | N/A | “Not provided by pharmaceutical sponsor, possibly because study stopped early due to unexpected side effects, and raw data may never have been compiled.” |
| 7 | FDA, Health Canada, NIOSH | Yes | Adverse event reports | No | “The data did not provide some of the detail we would have liked, such as indication for the drug, dosing etc. We summarized the results in narrative form but did not include in the quantitative analyses of the data we retrieved from published studies” |
| 8 | Clinical investigator, medical director of company | Yes | CSRs | Yes | “Assessed quality of the studies and extracted data for use in forest plots and description” |
| 9 | Clinical Study Data Request,EMA, FDA | Other\* | Case report forms | N/A | “N/A as data not received” |
| 10 | Clinical investigator, EMA, Pharmaceutical company | Other¥ | Details of trial participants at start of trial (baseline data and info about randomization) | No | “Only data at start of trial was available” |
| 11 | EMA, GSK and FDA  | Yes | Clinical and Statistical reviews at FDA, CSRs  | Yes | “We checked the data for consistency (across multiple published and unpublished sources) and reported in the systematic review the most accurate and conservative estimates. If needed, we contacted authors for confirmation” |
| 12 | Pharmaceutical company | Yes | CSRs, IPD | Yes | “Data from CSRs & IPD were used in evidence synthesis”“We know patient level data exists but we were not given access to it despite trying'' |
| 13 | Pfizer | Other\* | CSRs | N/A€ | “Extraction of data from Pfizer Medical Information Report” |
| 14 | EMA, FDA | Yes | CSRs, protocol with appendices | Yes | “We extracted, compared and used the aggregated effect estimates data for predefined outcomes” |
| 15 | Helsinn, Merck and Pfizer  | Yes | CSRs | Yes | “Where possible incorporated it as more likely to be the correct data than what was published” |
| 16 | EMA, FDA | Yes | FDA medical and statistical reviews | Yes | “Performed data extraction from these sources. Compared with data from published sources” |
| 17 | EMA, NIOSH | Yes | N/A | No | “Excluded studies” |
| 18 | FDA | Yes | CSRs, FDA reports and IPD | Yes | “Data was used in place of publication” |
| 19 | YODA | Yes | CSRs | Yes | “Data were used in network meta-analyses” |
| 20 | Bristol-Myers Squibb, Genentech, Schering-Plough | Yes | CSRs | No | “In narrative synthesis. However, some of the data/text needed to be removed before the final technology assessment report is published under the confidentiality agreement”. |

N/A: not applicable, FDA: food and drug administration, EMA: European medicine agency; NIOSH: The National Institute for Occupational Safety and Health

βResponse: “data not provided by pharmaceutical sponsor possibly because study was stopped early due to unexpected side effects and therefore the raw data may not have been complied”.

\*Still awaiting data/updating review; ¥Intendeddata requested was not available; €Intend to incorporate data in a meta-analysis.

**Table 3: Barriers when seeking regulatory data for use in a Cochrane review**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Requested / used regulatory data** | **Considered regulatory data** | **Not considered regulatory data** |
| **Survey question** | **Total no. of responses: n (% of total responses)** |
| Are there any barriers to using regulatory data? | n=20 | n=7 | n=133 |
| Yes | 14 (70) | 6 (86) | 67 (50) |
| No | 2 (10) | 0 (0) | 10 (8) |
| Unsure | 4 (20) | 1 (14) | 56 (42) |
| What were these barriers? | n=14 | n=5 | n=60 |
| Restricted and limited sharing of data | 8 | 4 | 31 |
| Time-constraints  | 6 | 2 | 17 |
| Lack of experience (inc. statistical) | 4 | 1 | 21 |
| Identifying/searching for trials | 2 | 1 | 13 |
| Quality of data | 1 | 0 | 12 |
| Cost | 0 | 1 | 1 |
| Effort/resources required | 0 | 0 | 5 |
| Limited access for peer reviewers\* | 0 | 0 | 1 |

**\***This referred to peer reviewers not having access to regulatory data during the peer review stage.

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