Dear Editorial Team,

Thank you for the opportunity to revise our manuscript. We respond in detail to all the comments below and indicate changes made in the paper. We have submitted a version of the paper with Track Changes shown. We feel that these comments have improved the paper. We look forward to hearing from you soon.

Associate Editor’s Comments

1. This study appears to be part of another study that was submitted to the BMJ. Please outline clearly what the differences are between the manuscripts.

RESPONSE: The study that was recently accepted by BMJ is a separate study and differs from this one in several ways.

i. Different study designs and data: This is a qualitative interview study using semi-structured open ended questions. The BMJ paper was a quantitative cross-sectional electronic survey.

ii. Different study populations: This project included participants who have conducted systematic reviews outside of The Cochrane Collaboration as well as those who have published Cochrane Reviews. The BMJ study surveyed only Cochrane authors and included many more Cochrane authors than the in depth interviews.

iii. Different aims: The aims of this study were (1) to understand the experience of authors conducting systematic reviews attempting to obtain unpublished data for their reviews, and (2) to understand the importance of the use of unpublished data in systematic reviews and how the inclusion of that data can affect the review. The objective of the BMJ study was to survey Cochrane authors about whether and how they search for unpublished data.

iv. Different research teams: The first author of the project submitted to BMJ (Schroll) was not involved in this project and the first author of this project (Wolfe) was not involved in the BMJ project.

2. The method section in the abstract should describe the sampling strategy
given the small number of participants amongst the thousands of eligible authors.

RESPONSE: We have added the following text to the abstract:

“.... authors of systematic reviews who have published Cochrane reviews or published systematic reviews outside of The Cochrane Library. We included participants that 1) were the first or senior author of a completed, published systematic review of a drug intervention, 2) had expertise in conducting systematic reviews and meta-analyses, searching for published and unpublished data, and assessing methodological biases, and 3) were able to participate in an interview in English. We excluded potential participants who were authors of reviews of devices or interventions other than drugs. We used non-random sampling techniques to identify potential participants who had the knowledge and professional experience to address the aims of our study. We selected systematic review authors that met our inclusion criteria with the aim of achieving diversity of research topic area and geographical location. Two hundred Cochrane authors agreed to be interviewed for this study and 32 met our inclusion criteria. We randomly selected 18 of these for initial contact; 2 did not respond after two attempts and 16 agreed to be interviewed (89% response rate). The researchers outside of the Cochrane Collaboration were chosen using non-random and snowball sampling. Twenty-four non-Cochrane authors were contacted; four replied that they could not participate, four did not respond, and 16 were interviewed (67% response rate).”

3. The abstract should provide more examples of strategies that the review authors have actually used, just stating that "Respondents described a variety of methods..." is not informative.

RESPONSE: We have added the following text to the abstract: “Respondents described the collaboration with other colleagues and/or students required to organize, manage, and use the data in their reviews, generally developing and using templates, spreadsheets, and computer programs for data extraction and analysis.”

4. It is not clear how the conclusion that "increased availability of trial data from the European Medicines Agency are a step towards making it easier to acquire critical drug data" follow from presented survey data.

RESPONSE: As noted in the abstract and methods, this study was a qualitative analysis of semi-structured, open-ended in-depth interviews, not survey data. This statement flows directly from the interviews of our respondents who discussed the progress at the EMA. The sentiment is that since the EMA is such a large and influential organization, any changes it makes could potentially be adopted by the FDA or other similar regulatory agencies. We have clarified the text in the abstract as follows: “Recent actions by government, such as increased availability of trial data from the European Medicines Agency, may make it easier to acquire critical drug trial data in the future”.

5. The manuscript method section claims that all first authors of Cochrane reviews were surveyed. Please provide the number of authors approached and
the method used to identify authors.

RESPONSE: We could not find any text stating that all first authors of Cochrane reviews were surveyed for this study. We have clarified that 200 Cochrane authors agreed to be interviewed. See rewritten “sampling” section in methods section, page 5.

6. The inclusion criteria for Cochrane authors should be described in more detail.

RESPONSE: We have clarified the text in the methods section under “sampling” (page 5). It is important to note that these were purposive sampling techniques that are typically used for in-depth interviews. We were not attempting to achieve a random sample.

7. The definition of unpublished data should be tabulated and frequencies should be reported.

RESPONSE: We have carefully considered this suggestion, but tabulating frequencies is inappropriate for this type of study. As described in the methods section, our participant sample was a non-random sample, not a random, representative sample. Given our interpretive analytic approach which seeks to explain and understand how systematic reviewers seek data, reporting frequencies would erroneously suggest that we could tally standardized responses from our interviewees as one would do with a survey. This was not a survey where a narrow set of the same questions were asked in the same order for each interview, which would allow us to provide a more quantitative analysis of our responses. Given our analytic methods, it is not clear how one would meaningfully evaluate the difference between 10 participants making a comment about a particular theme and 8 participants making a comment about the same or a different theme. We could re-analyze our data to calculate frequencies, but we believe this would not increase the validity of our study and would suggest naïveté to readers who might be familiar with qualitative research methods. For more information on qualitative sampling and analysis, please refer to our references #17 (Creswell, J.W., Qualitative Inquiry & Research Design: Choosing Among Five Approaches. Second Edition. Second ed. 2007, Thousand Oaks: Sage Publications) cited on page 7 of the manuscript.

In response to this comment, we have added additional definitions of unpublished data as described by our participants (page 9, paras 1 – 3).

8. The frequencies for sources of unpublished data should be reported. It is unclear who the author of the opinions regarding advantages and disadvantages of sources were - this should be clarified.

RESPONSE: We have clarified that Table 2 is derived from the analysis of our participant responses. We have added the following text (page 9, para 1):

“The respondents’ choices of data sources are shown in Table 2. Our analysis of the interview data suggests that these choices were influenced by how they defined unpublished data, and whether they believed a source had the data and
would be willing to share them.”

9. The section "Unresponsiveness or refusal to share data" need to clarify that no primary authors were surveyed, outlined are systematic reviewers' beliefs about the reasons why primary authors do not respond to their requests.

RESPONSE: We have attempted to clarify that all the data in our paper are from our data source – the respondent interviews. We have rewritten the first sentence of this section as follows:

“There were three main reasons provided to our respondents as to why the study author(s) they contacted would not or did not provide the data our respondents were seeking.”

10. The paper would benefit from a general discussion section and the topic and implications of including unpublished data in systematic reviews should be discussed more broadly.

RESPONSE: The major themes derived from our data are described in the first paragraph of the results (page 8). We have relabeled the "Conclusion" to the “Discussion” as this is where the implications of our findings are discussed more broadly. This section discussed the pros and cons of various data sources, as well as the difficulties of including the data in reviews. We also discuss ways that obtaining access to drug trial data could be improved.

11. It is also not clear what the basis is for this statement "Respondents uniformly agreed that the benefit of identifying unpublished data was worth the effort and was necessary to identify the true harms and benefits of drugs".

RESPONSE: As noted above, all the data in this study are derived from the interviews of the respondents. Therefore, this statement is derived from our analysis of these data. Although it is not appropriate to calculate frequencies for qualitative data (see response to comment #7), it is appropriate to identify common themes or themes that are outliers. Therefore, we use the term “uniformly” because all respondents indicated that they believed it was important to identify unpublished data for reviews of drugs. There were no outliers for this particular theme.

12. The result section seems to highlight that systematic reviewers were generally unsuccessful in obtaining unpublished data or if they had them, the data were not usable. Furthermore, there was no mention of analyses that inclusion of unpublished data identified the "true harms and benefits of drugs".

RESPONSE: The statement in sentence 1 of this comment is correct, except, as noted in the results section, our respondents did use the data they identified, although it was difficult and required a lot of work (see Results "Using the data", pages 14-15)

The analyses supporting the statement that respondents believe that unpublished data are needed to identify the true harms and benefits of drugs are described in Results "public health" pages 16-17.
13. It might be better to combine the quantitative and qualitative results of this study rather than trying to publish them separately.

RESPONSE: These are two very separate studies. See response for comment #1

Reviewer Dhruva
Minor revisions
1. Introduction, first paragraph: "legal settlements" should most likely be changed to "legal action," given that some information is obtained in the discovery process as well.
RESPONSE: Made the change

2. Introduction, second paragraph: should add "In an effort to provide a more thorough picture" before the 3rd sentence starting "The Cochrane Collaboration is a major producer...”
RESPONSE: we did not make this change as it seemed awkward

3. Methods: the authors state that 200 Cochrane authors agreed to be interviewed. How many were asked?
RESPONSE: We have clarified in the methods section, under “sampling” that our starting point was 200 authors who agreed to be interviewed. Our human subjects approval did not permit us to contact individuals who did not agree to be interviewed.

4. Methods: the authors write "the investigators for this project identified authors of published systematic reviews." Can they detail the process of identifying such authors? Particularly the non-Cochrane authors? This would help us understand the background of their source of data
RESPONSE: We have edited and expanded the methods section, under “sampling” to address this comment.

5. Results: Was it 11 geographical regions or 11 countries?
RESPONSE: 6 geographical regions, 11 countries. This has been clarified in the paper (page 8).

6. Results, under section "Pharmaceutical companies." First paragraph, about 2/3 through, would change the word "excuses" to something less pejorative.
RESPONSE: changed to “reasons”

7. Results, under section "Regulatory agencies" Would be helpful to have a
discussion of thoughts on EMA here, as it is currently all focused on the FDA and then the EMA pops up in the discussion (and rightfully so), but is not discussed in the results

RESPONSE: As noted in the Discussion (page 18, para 2), our respondents spoke mostly about the FDA because that was where they had experience. Even our non-US respondents tended to go to the FDA site before they would go to the EMA. When respondents discussed the FDA, we did ask about experience with the EMA, though very few had any. The changes at EMA are quite recent, therefore it is understandable that our respondents had little experience with EMA. However, due to changes at the EMA making data more available to researchers, authors of reviews may begin to contact the EMA for data. Therefore, we mention this possibility in the discussion. If a study similar to this one is conducted in the future, we may be more likely to gather respondents’ descriptions of their experience with EMA.

Discretionary revisions
1. Introduction: can the authors provide an example of a case where our perception of a drug was changed by unpublished data? Perhaps one sentence to give an example (e.g. gabapentin as they have cited)

RESPONSE: We have added text and a reference to the introduction (page 4, para 2):

“There have been prominent cases of well known drugs, such as gabapentin, oseltamivir, and rofecoxib where the analysis of unpublished data revealed important insights about the benefits and harms of those drugs not previously identified in their initial publications [14].”

2. Results: it would be helpful if the authors explained how many systematic reviews were conducted by the 32 respondents, and the mean or median and range. This would give the reader a sense of the respondents' experience.

RESPONSE: We did not ask this of our respondents. We did ask them if they had experience conducting systematic reviews but we only required that they be a first or senior author on one systematic review.

3. Results, under section "Unresponsiveness or refusal to share data". In stating "the third reason was that authors wanted to maintain control..." There should be a statement stating that respondents believed this (since there is no evidence that an author told this to a respondent)

RESPONSE: We have modified this sentence to “The third reason noted by our respondents was …”

Reviewer Peinemann
Major compulsory revisions
1. I perceive the manuscript mainly as a compilation of statements by authors of
systematic reviews on the nature and handling of unpublished study data. I have the impression that some statements could be regarded as beliefs about others and even imputations aimed at other persons.

RESPONSE: This is a qualitative research project that aimed to understand the experience of systematic review authors who attempted to obtain unpublished data for their reviews, to understand the importance of the use of unpublished data in systematic reviews, and how the inclusion of that data can affect the review. Reporting the results of qualitative research is meant to include the voices of the participants to provide a better understanding of their experiences.

2. The contents reflect some of the daily routine associated with the conducting of systematic reviews. The search for and description of unpublished studies is very important to get a better picture of all efforts completed or ongoing to investigate an intervention.

RESPONSE: We appreciate the reviewer’s comments.

3. The knowledge of unpublished studies could relativize the conclusion of a report and could create hints at differences between published and unpublished trials. On the other hand, results from analyses conducted before the planned end of an observation period or before the planned number of participants has been recruited may be associated with an additional risk of bias. Interim reports and early discontinuation are examples of unfinished data analysis. A large proportion of unpublished studies may fall into this category. The question arises whether these data decrease or increase the risk of bias already possibly inherent in the included published studies of a systematic review. Should the data really be included if available? I think that this issue could be discussed.

RESPONSE: This issue is discussed in several places in the manuscript. First, as described in the section on “using the data” (page 14 – 15), our respondents went to considerable trouble to incorporate unpublished data into their reviews, for example, developing templates and protocols that were used to extract data and assess the risks of bias. These assessments determined whether the data would be included in their review. Under the section on “public health,” our respondents describe why they believe these data should be added to reviews.

We agree with this reviewer that assessing the risk of bias of studies with unpublished data is important and have added the following text to the Discussion section (para 1):

“After unpublished data were identified, our respondents found that considerable effort was needed to get the data into a format that could be used in the reviews. Not only does the numerical data need to be available, but reviewers must have sufficient information about the characteristics of the studies with unpublished data in order to be able to assess the risks of bias of these studies.”
Minor Essential Revisions

I would be interested if Cochrane authors had different problems, experiences, or opinions than Non-Cochrane authors. The authors of the present manuscript included 16 authors of Cochrane reviews and 16 authors of other reviews but I could not find a statement describing the difference between both groups. I would expect Cochrane authors to be specifically educated because of a prestructured template, strict rules, and a supportive review group provided by the Cochrane Collaboration.

RESPONSE: Although we interviewed both Cochrane and non-Cochrane reviewers in an attempt to have a variety of perspectives on obtaining unpublished data, as explained above, it is not meaningful in a study of this design to make such comparisons. One major difference between the two groups is their access to and use of The Cochrane Handbook. We have added a description of the type of advice provided by The Cochrane Handbook to the discussion section (page 21):

The Cochrane Handbook for Systematic reviews of Interventions [16] suggests identifying unpublished data by contacting experts, pharmaceutical companies, national and international trial registers (e.g. clinicaltrials.gov), and other specific trial registers. No specific guidance for searching for drug trials is provided and sources of drug trial data such as legal settlements, regulatory agencies, human subject approvals, and annual reports of funding agencies are not mentioned. In addition, little advice is provided in the Cochrane Handbook or elsewhere about strategies for obtaining the data from different data sources. Future revisions of The Cochrane Handbook should take into account reviewers’ experience with obtaining unpublished drug study data from regulatory agencies.

Discretionary Revisions

Reading of this could be facilitated by providing a flow-chart or a little bit clearer description of searching and including authors: number of contacted persons; number of eligible authors, separate for Cochrane authors and authors of other reviews

RESPONSE: we have added a Flowchart, referenced on page 6 at the end of the 1st paragraph.