PEER REVIEW HISTORY

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This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports
AUTHORS	Doshi, Peter; Jefferson, Tom

VERSION 1 - REVIEW

REVIEWER	Ross, Joseph Yale University School of Medicine, Internal Medicine
REVIEW RETURNED	07-Nov-2012

GENERAL COMMENTS	In this manuscript, Doshi and Jefferson search public data sources and file Freedom of Information Act requests to obtain clinical study reports (CSRs) which they then descriptively explore in an effort to guide clinicians and systematic reviewers and inform evidence based medicine. While I am strongly supportive of better understanding the use of additional data sources such as CSRs to ensure better systematic reviews and summary analysis of clinical trial research, I do not think this research project achieved its maximum potential impact. Originality and Importance The investigators descriptively analyze 78 CSRs of 14 pharmaceuticals, providing information on page length and presence of key sections of information. While such a description has not been done previously to my knowledge, it does not provide sufficient insights to advance the field. This past January, Wieseler and colleagues published their findings in BMJ (2012;344:d8141) that demonstrated that CSRs reported higher quality information for clinical trials when compared with publications or results reporting systems. Their study was limited by the inaccessibility of CSRs for many of the comparisons they conducted. I had hoped that this study would advance the field further by making a comparison of this sort for a complete sample of study article-CSR pairs. Instead, the investigators predominantly focus their analysis on descriptive information and imply the significance of missing information for systematic reviewers and summary analysis, without proving the impact of the absence. I strongly agree that the

	information missing is likely to be consequential, but as a research project, the purpose is to generate evidence that proves or disproves the hypothesis. Moreover, some of the investigators conclusions are focused on what is missing from CSRs. But it is unclear what the implication of missing that information is for the field. Scientific Reliability The investigators explain that they did an exploratory review with a long-term intention of improving the credibility of research synthesis. I think the research question could be more clearly defined. It is not clear what the purpose of exploring the structure and content of CSRs, how new insights would be gained from this research, and so forth. I am also not clear how this research is “exploratory”. That term is usually reserved for qualitative research that seeks to generate hypotheses, rather than test hypotheses. Although the investigators do not state an explicit hypothesis, neither are they using qualitative methods to develop one. Overall Design of Study I am concerned about the sample of trials used for analysis. By using a non-random sample, the findings are not generalizable. Moreover, more than a third were obtained from the investigators Tamiflu work, which they have already discussed in great detail in previous articles (PLoS Med 9(4): e1001201). A stronger study would include a larger number of CSRs, ideally all from more recent time periods after ICH E3 approval (why include the 4 written prior?). 78 CSRs is a very small number. Moreover, given the number of products for which documents have been produced as part of litigation, it is likely that more CSRs are available in the UCSF DIDA web-base or in other places. Methods More methodological information would be useful. For instance, in the 5 steps for obtaining CSRs, I had a number of questions. How were CSRs identified for downloading on the internet? How were additional investigators identified for correspondence about CSRs obtained via Freedom of Information Act requests? What CSRs were manufacturers approached about? I am not sure that I agree with the investigators contention that there is no known sampling frame to obtain CSRs. I would expect that a CSR would have been generated for every trial conducted as part of an application to a pharmaceutical regulator like the FDA or EMA. From regulator documents, all phase III trials could be identified and CSRs could have been requested.

	Why did the investigators not simply abstract the information requested by ICH E3? Or maybe they did, but the text suggests to me that they developed their own abstraction form. The compression factor objective was not established in the Introduction and the Methods are unclear, particularly the generation of "conservative" versus "realistic" compression factors. How many were inaccessible? Results The results are predominantly focused on page length and presence of content; a deeper analysis is necessary to provide new insight for the field. The new knowledge that is generated by the study is not convincing that key information is being lost when reporting clinical trial results in a CSR format as opposed to a journal article. Given the narrow focus of the results, perhaps this article would be better structured as a research letter. Interpretation and Conclusions I thought the interpretation and conclusions, of the manuscript text and the abstract, went well beyond the data presented. The investigators engaged in a substantial amount of editorializing, which detracts from the objectivity of their research. I would suggest a full re-write of these sections that were focused on summarizing their findings and clarifying the implications for the field. For instance, the 2nd paragraph of the results states "[CSRs] far surpass the level of detail available in journal publications …" Any reader would assume this to be true based on a general understanding of the field, so this statement could be appropriately made in a commentary. However, the purpose of this article was to examine this question – and no measurable comparison to journal article content was made (to assess the level of detail), just journal article length. So this statement, in the context of this article, is unproven. Abstract The abstract should only make reference to the 78 CSRs that were the sample for the analysis.

REVIEWER	Scherer, Roberta Johns Hopkins Bloomberg School of Public Health, Epidemiology
REVIEW RETURNED	12-Nov-2012

GENERAL COMMENTS	The authors of this report were able to obtain 84 Clinical Study Reports (CSR) from a variety of sources, and have reviewed the

	contents of 78, assessing whether specific sections as recommended by International Committee on Harmonisation were included in the report and noting the length of the various sections when included in the report. Given that the decision by the European Medicines Agency to allow public access to these reports was made late in 2010, there is little current work in the literature on describing the contents. Other than sporadic articles on individual reports obtained through litigation, I am aware of only one report in the literature (Weiseler et al BMJ 2012 which the authors cite). It is likely that a great deal of effort was required to obtain the number of reports presented in this paper. This work is original and so adds to the current state of understanding in this field. The authors argue that access to CSR will allow systematic reviewers to obtain trial information in more detail than can presently be obtained through journal articles. They state that little is known about the structure and content and aimed to describe what was included is a report. In this sense this information is of general use and of special interest to those persons performing and using systematic reviews of drug interventions. By its nature, however, this study cannot address the inadequacies of reporting other types of trials nor will it likely be of specific interest to practitioners. It would be helpful if the author explicitly describe their definition of “adequate” for purposes of inclusion of a CSR in this report. They do say “too fragmentary” but that is somewhat vague. Using a detailed extraction form, the authors scored the presence of each of the sections recommended by the ICH, either by direct observation or by noting the table of contents, and then recorded the page length of each section. The study is straightforward and the authors have appropriately audited each others’ extraction as a check for bias. I found that the authors make a fairly large assumption, however, in that they equate the length of a section (in number of pages) with the amount of detail that is provided by the report. While this assumption may be true, there is no data to support it. For example, although the number of pages in a typical journal trial report may be equivalent from article to article, the trial elements reported may vary widely. While page length might well be a reasonable surrogate for “amount of detail” I would have liked to have seen at least one or two direct comparisons to support this claim. Possibly, the information from Weiseler would support this assumption, but the authors do not describe it. Because of this, I did not find the “compression factor” (a measure of the ratio of number of pages in a journal report to that in the CSR) to be a particularly useful measure and I wasn’t sure how to interpret it, especially the “conservative” vs the “realistic” factors. Further, the authors are over-interpreting the data when they say “The median length of 644 pages for reports in this study confirms that CSRs are the most detailed and complete, integrated form of reporting of the design, conduct and results of clinical trials” [line

	218-220] when all they have shown is the number of pages in the report. This conclusion is based completely on the equation that page length is proportional to amount of detail and the authors provide no evidence in the paper or in the cited literature to support this assumption. The authors also note the presence of individual case report forms available in one of the CSRs. Although the authors perceive the presence of individual patient data to be a good thing, it would be important to consider safeguards in place to protect patient confidentiality. For example, is there any assurance that the data have been correctly de-identified beyond simply changing the study ID. In the discussion, lines 302-304, the authors should note that the presence of open access journals increase the possibility of more detailed reporting in journal articles so that trial reports may no longer be "limited to summary and aggregate details" Some minor issues: Line 119: Not quite a mixed metaphor says that "lack of visibility may also conceal" Line 191: sentence is unclear (are there words missing?). Also in that paragraph, there are some "of''s" that should not be present (e.g. line 194) Line 281 – too many periods

- This manuscript received three reviews at The BMJ but the third referee had declined to make his review public.

9.	Reviewer: 2		
10.	In this manuscript, Doshi and Jefferson search public data sources and file Freedom of Information Act requests to obtain clinical study reports (CSRs) which they then descriptively explore in an effort to guide clinicians and systematic reviewers and inform evidence based medicine. While I am strongly supportive of better understanding the use of additional data sources such as CSRs to ensure better systematic reviews and summary analysis of clinical trial research, I do not think this research project achieved its maximum potential impact.		No action taken
11.	Originality and Importance The investigators descriptively analyze 78 CSRs of 14 pharmaceuticals, providing information on page length and presence of key sections of information. While such a description has not been done previously to my knowledge, it does not provide sufficient insights to advance the field. This past January, Wieseler and colleagues published their findings in BMJ (2012;344:d8141) that demonstrated that CSRs reported higher quality information for clinical trials when compared with publications or results reporting systems. Their study was limited by the inaccessibility of CSRs for many of the comparisons they conducted. I had hoped that this study would advance the field further by making a comparison of this sort	In classical evidence synthesis theory exploration and description (what sometimes is now called scoping) always precedes synthesis and analysis Light RJ, Pillemer DB (1984). Summing up. Cambridge: Harvard University Press. This is the purpose of our review: a focus on exploration and description (not analyses such as comparison to	No action

	for a complete sample of study article-CSR pairs.	publications). We made this choice for the very reason that all reviewers acknowledge: it is a new field to 99.9% of readers.	
12.	Instead, the investigators predominantly focus their analysis on descriptive information and imply the significance of missing information for systematic reviewers and summary analysis, without proving the impact of the absence. I strongly agree that the information missing is likely to be consequential, but as a research project, the purpose is to generate evidence that proves or disproves the hypothesis.	Our purpose was not to analyze or and test anything. It was to systematically capture the extent of information that has been hidden but is now increasingly publicly accessible thanks to the European Medicines Agency. We want readers to learn that CSRs are available, and that behind every ten page journal article there are thousands of pages of regulatory documents for the very same trial.	No action
13.	Moreover, some of the investigators conclusions are focused on what is missing from CSRs. But it is unclear what the implication of missing that information is for the field.	We agree. Like in our Tamiflu Cochrane review one is left guessing whether what you see is consistent with what you cannot see. The implication is that missing data threatens to possibly invalidate our current medical evidence knowledge base.	No action
14.	Scientific Reliability The investigators explain that they did an exploratory review with a long-term intention of improving the credibility of research synthesis. I think the research question could be more clearly defined. It is not clear what the purpose of exploring the structure and content of CSRs, how new insights would be gained from this research, and so forth.	We have tried to clarify the purpose of the research. Also please see ser. 11 & 12.	We have added the sentence: “We carried out an exploratory review to describe the structure and content of a non-random sample of clinical study reports. By describing the contents of CSRs, this research seeks to transform CSRs from an obscure document only known to regulators and industry into a more widely known and accessible document. Our long-

			term intention is to improve the credibility of research synthesis by facilitating a move from the level of detail found in journal articles to the level of detail found in regulatory documents, thus guiding clinicians and other decision makers at all levels."
15.	I am also not clear how this research is "exploratory". That term is usually reserved for qualitative research that seeks to generate hypotheses, rather than test hypotheses. Although the investigators do not state an explicit hypothesis, neither are they using qualitative methods to develop one.	We did not mean to link our study to "explorative" studies such as in large dataset epidemiology studies. Here we mean exploration as description. "Descriptive review" may be a better term, but we are not sure. We used "exploration" as we felt we were exploring a hitherto unknown continent -- CSRs.	We would like the editors' view on the best adjective to use in the study title.
16.	Overall Design of Study I am concerned about the sample of trials used for analysis. By using a non-random sample, the findings are not generalizable. Moreover, more than a third were obtained from the investigators Tamiflu work, which they have already discussed in great detail in previous articles (PLoS Med 9(4): e1001201).	We have made edits to try to emphasize the limitations regarding generalizability. Regarding our non-random sample: we used what we could find. There was no way to do a random sample as we do not know the denominator of all CSRs that exist. We do not even have a list of the CSRs in EMA's possession. We therefore used all CSRs in our possession from prior research (Tamiflu, Relenza) and what we thought would be a useful and admittedly non-random sample of CSRs related to the 10 top	To more strongly emphasize limitations, we have moved this paragraph to the top of the Discussion section and edited it as follows: "Despite the ~~apparent~~ size of our non-random sample, ~~we are not sure~~it is unclear whether our conclusions are ~~broadly~~ generalisable to all other CSRs because we have extremely limited knowledge about the total population of CSRs in regulators' and sponsors' possession. Nevertheless, within our sample spanning different manufacturers, therapeutic classes, and times, we found that the structure of CSRs was, within different house styles of presentation, strikingly similar ~~across medical products and sponsors~~, probably ~~thanks~~due to the existence of ICH~~'s~~ E3.[37] This suggests that the structure and content of other CSRs is likely to be similar."

		drugs.	
17.	A stronger study would include a larger number of CSRs, ideally all from more recent time periods after ICH E3 approval (why include the 4 written prior?). 78 CSRs is a very small number. Moreover, given the number of products for which documents have been produced as part of litigation, it is likely that more CSRs are available in the UCSF DIDA web-base or in other places.	We accept that some might regard 78 as too small a sample. We did search DIDA for CSRs and the one referenced CSR (Vioxx) was all we could discover. In the end, we think 78 CSRs is an acceptable number that supports our conclusions.	No action
18.	Methods More methodological information would be useful. For instance, in the 5 steps for obtaining CSRs, I had a number of questions. How were CSRs identified for downloading on the internet? How were additional investigators identified for correspondence about CSRs obtained via Freedom of Information Act requests? What CSRs were manufacturers approached about?	We have included additional information about the methods in the text.	The text now reads: 1. Requesting from EMA, under its freedom of information (FOI) policy, CSRs for manufacturer sponsored trials of the 10 best-selling prescription-bound products in the United States in 2010.[23] 2. Reusing CSRs from our own previous research (oseltamivir, zanamivir)[12] 3. Downloading CSRs openly available on the Internet. Search terms were not predefined, but sites searched included Google (http://www.google.com), the Drug Industry Document Archive (http://dida.library.ucsf.edu/), and IQWIG's library of reboxetine studies (https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html) 4. Corresponding with one researcher who obtained CSRs through a FOI request to FDA (epoetin alfa) 5. Requesting manufacturers fill any gaps in the completeness of reports that we believe are legally required to be

			publicly available (paroxetine).
19.	I am not sure that I agree with the investigators contention that there is no known sampling frame to obtain CSRs. I would expect that a CSR would have been generated for every trial conducted as part of an application to a pharmaceutical regulator like the FDA or EMA. From regulator documents, all phase III trials could be identified and CSRs could have been requested.	At the time we carried out the study, our understanding of FOI requests was that one had to make a specific request for a specific document. From our experience with a Cochrane review of neuraminidase inhibitors (Tamiflu and Relenza) we have learned that regulatory summaries such as medical officer reviews or European Public Assessment Reports, do not contain a complete list of all the trials that the regulator holds on a drug. For the CSRs requested from EMA (the top 10 drugs), we in fact did create lists of trials based on FDA documents (which are more comprehensive than EMA EPARs) and then submitted a FOI request to EMA to see which of these trials they held. However this does not mean that EMA does not hold additional trials on these drugs, and it does not mean our lists were complete. Therefore we do not have a real sampling frame. Furthermore, what EMA (or any other regulator) has in its holdings is arguably a biased sampling frame, because	No action

		regulators do not hold all CSRs, as we have documented in our other publication relating to Tamiflu and others have shown in other cases (Vedula et al. Trials. 2012 Aug 13;13(1):136.)	
20.	Why did the investigators not simply abstract the information requested by ICH E3? Or maybe they did, but the text suggests to me that they developed their own abstraction form.	We did abstract the information requested by ICH E3. We have given a copy of the blank extraction sheet we developed and use in Appendix 2. What we developed is directly based off of the elements that are specified in ICH E3, and what we present in the paper is a subset of elements that will be familiar and relevant to those who read reports of trials in journal publications such as systematic reviewers. We had to develop our own actual form, however, because E3 is not a form, it is a guidance document. The text at page 7 states "Our uncorrected (original) and corrected extraction sheets as well as audit records are available upon request from the corresponding author."	Have tried to make this point clearer by editing the sentence: "We created a list of around 40 potential sections we expected to find, generated directly from elements specified in E3."
21.	The compression factor objective was not established in the Introduction and the Methods are unclear, particularly the generation of "conservative" versus "realistic" compression factors. How many were inaccessible?	We have tried to clarify.	We have added a sentence to the Methods section stating: "The objective of this metric was to convey a rough sense of how much information present in CSRs may be being condensed ("compressed") in short journal publications, in consideration of CSRs' far

			greater length and level of detail." We have edited the description to help clarify the difference and explain their generation, as follows: "Because in most cases we could not access all parts of all CSRs (and therefore do not know their complete page length), we calculated "conservative" compression factors as well as "realistic" compression factors. "Conservative" compression factors were calculated on a trial by trial basis using the total number of pages in CSRs available to us divided by the length of journal reports for that same trial, while "realistic" compression factors were based on the true total page length of the CSR."
22.	Results The results are predominantly focused on page length and presence of content; a deeper analysis is necessary to provide new insight for the field. The new knowledge that is generated by the study is not convincing that key information is being lost when reporting clinical trial results in a CSR format as opposed to a journal article.	Whether or not key information is being lost will depend on the particular trial that is being analyzed and the purposes with which a reader is approaching a trial report. For example, for many readers, a journal length publication contains too much detail and just an 300-word abstract will suffice. For systematic reviewers, lowering "risk of bias" among included trials entails having access to more detailed information than is present in journal-length publications. Details of randomization and allocation	No action

		concealment are often complex and not easily described in journal articles, but are detailed in CSRs. Nonetheless, our focus in this study was on CSRs and we intend to carry out a more detailed comparison of CSR to journal article. This study however does report that CSRs often do contain elements (such as a trial Protocol) that would absolutely be of interest and benefit to systematic reviewers.	
23.			
24.	Given the narrow focus of the results, perhaps this article would be better structured as a research letter.	After discussion with Richard Sands this comment has been ignored.	No action
25.	Interpretation and Conclusions I thought the interpretation and conclusions, of the manuscript text and the abstract, went well beyond the data presented. The investigators engaged in a substantial amount of editorializing, which detracts from the objectivity of their research. I would suggest a full re-write of these sections that were focused on summarizing their findings and clarifying the implications for the field.	Our hope was that the contextualization and analysis we provide in the Discussion section be seen as a strength of the study, not a weakness.	No action, but we would welcome specific suggestions as to which areas are problematic or go beyond the data presented.
26.	For instance, the 2nd paragraph of the results states "[CSRs] far surpass the level of detail available in journal publications …" Any reader would assume this to be true based on a general understanding of the field, so this statement could be appropriately made in a commentary. However, the purpose of this article was to examine this question – and no measurable comparison to journal article content was made (to assess the level of detail), just journal article length. So this statement, in	We have used page length as a measure of level of detail. As another reviewer has provided a detailed critique of this issue, we have responded there in more detail. See serial 31.	See serial 31.

	the context of this article, is unproven.		
27.	Abstract The abstract should only make reference to the 78 CSRs that were the sample for the analysis.	Fixed.	The Abstract Results now read: "**Results:** We assembled a population of 78 CSRs (covering 90 RCTs; 144,610 pages total) dated 1991-2011 of 14 pharmaceuticals. ~~78 were adequate~~"
	Reviewer: 3		
28.	The authors of this report were able to obtain 84 Clinical Study Reports (CSR) from a variety of sources, and have reviewed the contents of 78, assessing whether specific sections as recommended by International Committee on Harmonisation were included in the report and noting the length of the various sections when included in the report.	No comment	No action
29.	Given that the decision by the European Medicines Agency to allow public access to these reports was made late in 2010, there is little current work in the literature on describing the contents. Other than sporadic articles on individual reports obtained through litigation, I am aware of only one report in the literature (Weiseler et al BMJ 2012 which the authors cite). It is likely that a great deal of effort was required to obtain the number of reports presented in this paper. This work is original and so adds to the current state of understanding in this field.	Thank you	
30.	The authors argue that access to CSR will allow systematic reviewers to obtain trial information in more detail than can presently be obtained through journal articles. They state that little is known about the structure and content and aimed to describe what was included is a report. In this sense this information is of general use and of special interest to those persons performing and using systematic reviews of drug interventions. By its nature, however, this study cannot address the inadequacies of reporting other types of trials nor will it likely be of specific interest to practitioners.	This is an important limitation which we have now added to the Discussion section.	We have added a sentence to the discussion: "Another significant limitation is that CSRs are only written for therapeutic, prophylactic, or diagnostic agents, and therefore inadequacies remain in evidence synthesis of other types of interventions such as surgical or behavioral interventions."
31.	It would be helpful if the author explicitly describe their	We have worked to improve our	"adequate" has been deleted from the

	definition of “adequate” for purposes of inclusion of a CSR in this report. They do say “too fragmentary” but that is somewhat vague. Using a detailed extraction form, the authors scored the presence of each of the sections recommended by the ICH, either by direct observation or by noting the table of contents, and then recorded the page length of each section. The study is straightforward and the authors have appropriately audited each others’ extraction as a check for bias. I found that the authors make a fairly large assumption, however, in that they equate the length of a section (in number of pages) with the amount of detail that is provided by the report. While this assumption may be true, there is no data to support it. For example, although the number of pages in a typical journal trial report may be equivalent from article to article, the trial elements reported may vary widely. While page length might well be a reasonable surrogate for “amount of detail” I would have liked to have seen at least one or two direct comparisons to support this claim. Possibly, the information from Weiseler would support this assumption, but the authors do not describe it.	description of the use of page counts, and have also included a more direct reference to the Wieseler work.	abstract. Regarding our use of page counts, we have written in Methods: “Size (page length) reflects the level of detail as well as the presence of many elements such as protocols and their amendments, randomization lists, statistical analysis plans, certificates of analysis and extra datation on subpopulations. We have demonstrated that these elements are essential for understanding and appraising a trial. The compression factor is a crude measure of how much is compressed or simply left out of each publication which will affect the reliability of the appraisal and interpretation of trials.” The text in Results to which the reviewer alludes has been edited as follows: “We excluded documents which ~~were too fragmentary to evaluate~~ were sections of CSRs but nonetheless contained insufficient information to understand the overall content of the CSR …” The reference to the Wieselser work (Discussion section) reads: “In a study that directly compared the adequacy of reporting between journal articles and CSRs, the authors found that complete information regarding greater than 40% of methods items were only available in CSRs.”

			We have also given two direct comparisons using word counts as well: "For example, the ratio of words in Protocol of the CSR for Aripiprazole CN138135 to the Methods section for published journal article of the same trial is 30.5 (53,713 words in the CSR Protocol versus 1,763 words in the journal article). For the oseltamivir WP16263 trial, the ratio was 22.7 (26,461 words in the CSR Protocol and amendments versus 1,177 words in the journal article)."
32.	Because of this, I did not find the "compression factor" (a measure of the ratio of number of pages in a journal report to that in the CSR) to be a particularly useful measure and I wasn't sure how to interpret it, especially the "conservative" vs the "realistic" factors. Further, the authors are over-interpreting the data when they say "The median length of 644 pages for reports in this study confirms that CSRs are the most detailed and complete, integrated form of reporting of the design, conduct and results of clinical trials" [line 218-220] when all they have shown is the number of pages in the report. This conclusion is based completely on the equation that page length is proportional to amount of detail and the authors provide no evidence in the paper or in the cited literature to support this assumption.	We have toned down the sentence, and added further detail.	The text (Discussion) now reads: "The median length of 644 pages for reports in this study, as well as CSRs' routine inclusion of trials' protocol, statistical analysis plans, and blank case report forms, strongly suggests that CSRs are the most detailed and complete, integrated form of reporting of the design, conduct, and results of clinical trials."
33.	The authors also note the presence of individual case report forms available in one of the CSRs. Although the authors perceive the presence of individual patient data to be a good thing, it would be important to consider safeguards in place to protect patient confidentiality. For example, is there any assurance that the data have been correctly de-identified beyond simply changing the study ID.	It is beyond the scope of the paper to come to conclusions on this issue, but we have added language to point out that there is an EMA working group focused on the topic of clinical trial data and protecting participant confidentiality.	The text now reads: "One manufacturer has claimed that the non-release of case report forms is motivated by concerns over protecting participant confidentiality.[38] Nothing we have seen so far corroborates this claim, however an ongoing EMA working group is specifically discussing issues related to protecting participant confidentiality. Based on current document releases and position statements, however, it appears that EMA has deemed

			case report forms and individual patient listings to be, in principle, releasable in their entirety (after a preliminary review)."
34.	In the discussion, lines 302-304, the authors should note that the presence of open access journals increase the possibility of more detailed reporting in journal articles so that trial reports may no longer be "limited to summary and aggregate details" Some minor issues:	We agree with this observation and have added text as suggested.	The text now reads: "It should be noted, however, that many journals now have websites which enables them to make available extended content beyond what traditionally appears in the printed journal."
35.	Line 119: Not quite a mixed metaphor says that "lack of visibility may also conceal"	Ok	Now: "Lack of visibility may also hinder ~~hinderstanding of conceal~~ the complexity of the organization and reporting of clinical trials. "
36.	Line 191: sentence is unclear (are there words missing?). Also in that paragraph, there are some "of''s" that should not be present (e.g. line 194)	Corrections made.	Fixed.
37.	Line 281 – too many periods	Fixed.	OK