PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical Trial Data Sharing: Here's the Challenge
AUTHORS	Kochhar, Sonali; Knoppers, Bartha; Gamble, Carrol; Chant, Alan; Koplan, Jeffrey; Humphreys, Georgina

VERSION 1 - REVIEW

REVIEWER	Frank W. Rockhold, PhD Duke Clinical Research Institute Duke University Medical Center Durham, USA I am the IRP chair for SOAR, Advisor and Steering Committee Member for Vivli and one of the original sponsors and creators of what is now CSDR.
REVIEW RETURNED	02-Jul-2019

GENERAL COMMENTS	This is a useful update from the CSDR IRP and a good way to make data sharing more visible. I do feel the authors could be a bit more specific about recommendations for the community to improve based on their experience. I have a few comments to perhaps strengthen the message. page 3 Line 46 while policy 0070 does mandate IPD sharing sometime in the future, the FDA does not have a required policy yet. You should mention that in fact the NIH does now have a mandate. just to make sure the readers have the right expectations p 4 line 68-- of those rejected how many were vetoed by the sponsor? It is allowable under the CSDR governance and would you comment on whether that "veto" serves the purpose of transparency? page 6 line 112 In making suggestions to improve proposals how does science and benefit to the patient enter into this? Many platforms like YODA and SOAR have a scientific review to improve proposals- yet CSDR differs here- can you comment on how that added depth of review would help (or not)? page 6 line 121- do you really mean "legislation" that would be a country by country differing approach? seems to me the professional society approach would be more fruitful.

	page 6 line 127. The ability to get data from multiple sponsors was a step forward for CSDR and does raise the issue of differing standards among sponsors. I think you should comment on how having standards would facilitate access to data. This is a huge hurdle to true transparency and a comment from you on the value would helpful. Also CSDR does not allow (for the most part) downloading of datasets- has that ever come up in a request and how did you handle it? Any opinion on the value of that? Page 7 line 141- I agree the "commercial sensitivity" argument was always weak and proven to be so- thus should CSDR remove its ability for a sponsor veto? This would send a constructive message to academia on pushing them to disclose. page 8 line 155- could you be a bit more specific on what areas could improve as these recommendations would beneficial to all platforms.

REVIEWER	David L DeMets,PhD Department of Biostatistics and Medical Informatics School of Medicine and Public Health University of Wisconsin-Madison Madison, Wisconsin USA
REVIEW RETURNED	13-Jul-2019

GENERAL COMMENTS	BMJ Data Sharing Review Review of “Clinical Trial Data Sharing: Here’s the Challenge” The authors review the recent activity surrounding the sharing of data from completed clinical trials, indicating that the amount of such activity is less than what might have been expected. They suggest some possible reasons. When the Institute of Medicine (IOM) developed their report on maximizing benefits and minimizing risk regarding the sharing of data from completed clinical trials, the expectation was that this would bring about a substantial increase in such sharing. The initial push came not from funders, whether federal such as NIH or from industry, but from patient advocacy groups, independent disease oriented research foundations and other “research watch dog” groups who wanted to be sure that the published analysis of completed trials was trustworthy and did not represent bias from either investigators or funders. Industry did not push back seriously because they probably believed they could not afford to be accused of hiding anything. Investigators for completed studies, whether federally funded or industry funded, were not happy as they believed that this was their data, or at least shared with the patients who consented, and they should be entitled to a long moratorium on sharing so they could publish their scholarly work. However, NIH records demonstrated that an alarming number of federally funded clinical trials were never published, and many other secondary papers were published long after the primary paper was published. The implication was that investigators were sitting on their data too long. Regulatory agencies such as the EMA and the FDA now have requirements for data sharing and many leading medical journals

	also have similar requirements, some with a short time line after trial completion and the primary publication. Thus, this article is very timely in documenting that of the large number of clinical trials made available, over 3,000 completed trials but only a small percentage (15%) have ever been requested data sharing. A review panel for the data sharing platform Clinical Study Data Request (CSDR) have a mandate to reduce the barriers to access and re-use data while providing a review as to the appropriateness of the request for data. Of those requested, the CSDR approved 84%. Of those approved, 75% approximately have either published or are in the process. As the authors point out, curating data for other's use is a time consuming and expensive process, and can be justified only if the data from these trials are being put to good use. It is disappointing that there seems to be a serious underuse of these completed trials, despite the initial clamor. Some request that were approved were never even followed up to gain access. Using data from a completed trial to validate the published analysis is not an easy or straightforward process. Bristow et al (ref below) published their experience on going back to a medical device trial ten years or so after the primary paper was published to publish a full manuscript for a series of abstracts presented at meetings much earlier. As they describe, it was challenging after that much time had passed to even recreate the analysis for their own primary published paper. Details were forgotten on definitions, the data base had been slightly updated for a few events discovered in trial close out, some analytic code was not included in the main analytic analysis package, itc. This was for a trial in which they were the primary investigators and had coauthored the primary paper. Only because they had access to all of the documentation and extensive analytic software code that had been saved, were they able to succeed in reproducing the primary paper but a great deal of time and effort was required. With reluctance from investigators to share "their" clinical trial data, Loh and DeMets (see reference below) published a paper suggesting some incentives for such data sharing. Among those incentives was for the research team requesting data from completed trials was to approach the initial investigators to be coauthors/collaborators on further analyses conducted by an outside team. These original investigators would have better recall on undocumented details that all trials suffer. That collaboration would serve to improve the productivity and impact for the trial as well as the original investigators who often get very busy pursuing the next trail and do not have sufficient time to mine their recently completed trial. A few specific comments Line 70: authors refer to proposals that were turned down for inappropriate statistical methods. Can a few insights be provided? Line 84: Of those data sharing requests that were approved, publication from 76% (45% + 31%) seems pretty good. Problem is mainly so few requests. Line 96 Indeed curating clinical trial data is expensive and time consuming. Any information on what the experience to date has cost? Line 110: There must be some review process to at least provide assurance on patient confidentiality but the entire review process is not free. Perhaps parties interested in gaining access to completed trials do not have sufficient resources, financial and human expertise.

	Line 120 Many IRBs demand very specific protocols for investigator access to data from externally completed trials, sometimes even from those completed internally, and any change in the questions posed, data elements used or analytic approaches are subject to a new IRB request. This poses a barrier to data exploration and data mining. IRBs need to lighten up on this aspect, focusing on protecting patient confidentiality. Line 136: Median days for access is 190 days which seems like a long time but also reflects that sharing data is not a simple process. Inquiring investigators need to be aware of that reality Line 141: Of some relief is that to date, little if any competitive access by industry to data from completed trials has been observed, one of the major fears in the development of the IOM Report. Line 145: The authors comment that there has been no sharing of data from completed trials by academic funders (eg the NIH). This is consistent with the attitude by these investigators and funders that the data is "theirs". Even when the data is made accessible, as they claim, it is often not easy to gain such access. References Institute of Medicine. Sharing Clinical Trial Data Maximizing Benefits, Minimizing Risk. 2015. Accessed on 12 June 19 at http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2015/SharingData/DataSharingReportBrief Lo B & DeMets DL, Incentives for sharing their clinical trial data, NEJM, October 6, 2016 Bristow MR, Saxon LA, Feldman AM, Mei C, Anderson SA, DeMets DL: Lessons learned and insights gained in the design, analysis and outcomes of the COMPANION trial, J Am College Cardiology, 2016

VERSION 1 – AUTHOR RESPONSE

Many thanks for the thoughtful and useful suggestions from both reviewers. We have amended the text and address each specific point below each comment here.

Reviewer: 1

Reviewer Name: Frank W. Rockhold, PhD

page 3 Line 46 while policy 0070 does mandate IPD sharing sometime in the future, the FDA does not have a required policy yet. You should mention that in fact the NIH does now have a mandate. just to make sure the readers have the right expectations

We have changed the text to delete FDA mention and add NIH reference

p 4 line 68-- of those rejected how many were vetoed by the sponsor? It is allowable under the CSDR governance and would you comment on whether that "veto" serves the purpose of transparency?

We have added some text about zero use of the veto by sponsors

page 6 line 112 In making suggestions to improve proposals how does science and benefit to the patient enter into this? Many platforms like YODA and SOAR have a scientific review to improve proposals- yet CSDR differs here- can you comment on how that added depth of review would help (or not)?

CSDR does have scientific and patient benefit assessment of proposals, and we improve proposals with suggestions for changes before approval.

page 6 line 121- do you really mean "legislation" that would be a country by country differing approach? seems to me the professional society approach would be more fruitful.

We have changed the text to clarify our meaning

page 6 line 127. The ability to get data from multiple sponsors was a step forward for CSDR and does raise the issue of differing standards among sponsors. I think you should comment on how having standards would facilitate access to data. This is a huge hurdle to true transparency and a comment from you on the value would helpful. Also CSDR does not allow (for the most part) downloading of datasets- has that ever come up in a request and how did you handle it? Any opinion on the value of that?

We have added text on this important point, thanks for raising this issue

Page 7 line 141- I agree the "commercial sensitivity" argument was always weak and proven to be so- thus should CSDR remove its ability for a sponsor veto? This would send a constructive message to academia on pushing them to disclose.

Sponsors have never used the veto so we have added text to make that explicit

page 8 line 155- could you be a bit more specific on what areas could improve as these recommendations would beneficial to all platforms.

We have added text to the final paragraph, thank you for the suggestion

Reviewer: 2

Reviewer Name: David L DeMets,PhD

Line 70: authors refer to proposals that were turned down for inappropriate statistical methods. Can a few insights be provided?

We have added some text to provide examples

Line 84: Of those data sharing requests that were approved, publication from 76% (45% + 31%) seems pretty good. Problem is mainly so few requests.

Agreed

Line 96 Indeed curating clinical trial data is expensive and time consuming. Any information on what the experience to date has cost?

Each sponsor has a private contract with the secure analysis enviornment provider so we don't know exact costs.

Line 110: There must be some review process to at least provide assurance on patient confidentiality but the entire review process is not free. Perhaps parties interested in gaining access to completed trials do not have sufficient resources, financial and human expertise.

We have added text on the barrier for researchers in low resource settings, thanks for raising this issue

Line 120 Many IRBs demand very specific protocols for investigator access to data from externally completed trials, sometimes even from those completed internally, and any change in the questions posed, data elements used or analytic approaches are subject to a new IRB request. This poses a barrier to data exploration and data mining. IRBs need to lighten up on this aspect, focusing on protecting patient confidentiality.

We have amended the text slightly for this paragraph.

Line 136: Median days for access is 190 days which seems like a long time but also reflects that sharing data is not a simple process. Inquiring investigators need to be aware of that reality

CSDR are in the process of publishing process times on their website so it will be clear to new data requestors

Line 141: Of some relief is that to date, little if any competitive access by industry to data from completed trials has been observed, one of the major fears in the development of the IOM Report.

Agreed

Line 145: The authors comment that there has been no sharing of data from completed trials by academic funders (eg the NIH). This is consistent with the attitude by these investigators and funders that the data is “theirs”. Even when the data is made accessible, as they claim, it is often not easy to gain such access. Agreed

VERSION 2 – REVIEW

REVIEWER	Frank W. Rockhold Duke University, US Chair IRP for SOAR, Senior Advisor for Vivli, and one of the originators of what is now the CSDR platform
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	You have addressed all of my comments. Thank you.