Author’s response to reviews

Title: Responsible Data Sharing in International Health Research: A Systematic Review of Principles and Norms

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Author’s response to reviews:

Dear Dr. Raus,

Thank you very much for considering our paper titled “Responsible Data Sharing in International Health Research: A Systematic Review of Principles and Norms” for publication in BMC Medical Ethics. We were pleased to find out our manuscript was reviewed with such diligence by two independent reviewers.

As you already pointed out, the two reviewers came up with widely divergent recommendations (minor revisions versus rejection). We are very grateful that we are allowed to submit a revised version of our paper accompanied by a response to the reviewer comments.

We believe we can definitely improve our manuscript by making the necessary changes in response to the concerns of reviewer #1. Though reviewer #2 raises some valid points, we do not support the claim that our “approach has severe methodological flaws that undermine [our] conclusions”. For the points we disagree on with reviewer #2, we provide all the arguments necessary to defend our methodological choices.
On the following pages, we outline point-by-point responses to these comments. We hope the new version of our manuscript will meet your expectations for publication.

Yours sincerely,

Shona Kalkman

Editor’s Comments to Authors:

General impression: Two reviewers have looked at the paper and have come back with different analyses:

- The first reviewer is concerned with an issue about section 4 concerning anonymization and pseudonymization.

- The second reviewer raises several methodological issues, for example relating to the systematic nature of the systematic review.

I think it is only fair that you get the opportunity to revise your manuscript and/or react to the methodological issues raised.

Comment 1: One of the reviewers points to recent literature on data sharing guidelines such as: Blasimme, Alessandro, Marta Fadda, Manuel Schneider, and Effy Vayena. 2018. Data Sharing For Precision Medicine: Policy Lessons And Future Directions. Health Affairs 37: 702–709. doi:10.1377/hlthaff.2017.1558. It seems advisable to include references to this literature and to identify how one ties in with or differs from these other studies.

Authors’ response: This paper is indeed relevant to our work. Though the central question of the Blassime paper (Why has the “cultural shift” needed to align data sharing with the needs of medical science not yet occurred?) is different from ours, the paper does refer to themes that constitute ethical principles. Blassime and colleagues conclude that the “policy network [for health data sharing] is rather loosely connected, which suggests possible fragmentation of the
policy landscape”. Their content analysis of policy documents is said to confirm this claim as the three identified central themes—autonomy, privacy, data quality/curation—were not given equal consideration by the different organizations. We have now included references to this paper in the Discussion section (page 18) rather than in the original analysis, since it was discovered post hoc.

Reviewer #1 Comments to Authors:

General impression: This article provides both an excellent review of international data sharing norms and an insightful analysis. The regrouping of trends into four over-arching themes in especially helpful and original.

Comment 1: The only weakness is Section 4. Line 366 uses the term "outright contradiction" concerning data anonymization. A closer reading of the original texts/sources on anonymization reveals more granular and contextual approaches rather than contradictions. For example, irrespective of whether total anonymization is ever possible, the data sharing research context may well require pseudonymization for longitudinal studies or in those studies that wish to return results. Again, the conflation by the authors of anonymized, anonymous, pseudonymized and de-identified approaches is also evident in lines 390-406. As the GDPR rightly states "anonymous" data is not personal data so the legal obligations and protections of personal data do not apply. Most recommendations do not and cannot apply to "anonymous" data (line 394).

I would argue that rather than "sparse guidance" (line 390), the analysis points to a confusion in the meaning of the terms used to describe the degree and type of data de-identification and hence, could affect both the sharing and the confidentiality and security of that data. (See Phillips, M, Knoppers BM. The discombobulation of de-identification. Nature Biotechnology. 2016; 34(11); 1102-1103).

In short, the "Conclusions" section should be more nuanced. Rather than using terms such as "haphazard" or "contradictory", the language of "confusion" and "incoherence" in the terminology describing guidance on de-identification processes would be more appropriate. Overall, this confusion stands in contrast to the greater convergence and clarity of the emerging normative frameworks for data governance and sharing as illustrated by this excellent paper.
Authors’ response: We thank the referee for pointing out that Section 4 requires a more nuanced discussion of our findings. We now see that our choice of words transmits a different message than the one we should actually be conveying. We have made alterations to Section 4 in accordance with the referee’s helpful suggestions. First, we have taken out all the language that signals “confusion” and “incoherence” (pages 16 and 20). Second, we have rewritten the paragraph on anonymous data: we now stress that the GDPR does not apply to anonymous data and explain the difference between the different terms used in the reviewed sources (i.e., anonymized, anonymous, pseudonymized and de-identified approaches). Third, we have taken out the statement about “sparse guidance” and included the suggested wording with reference to the mentioned citation (pages 16 and 17).

Reviewer #2 Comments to Authors:

General impression: The authors of this paper state that they conducted a systematic review of principles and norms that are relevant in data sharing for international health research. The topic of international data sharing is of high importance and so are the regulatory frameworks that can support sharing. Despite the intention of the authors to contribute to the debate, unfortunately, their approach has severe methodological flaws that undermine their conclusions.

Authors’ response: We are highly appreciative of the thorough work the referee has put into reviewing our manuscript. The referee has raised a number of valid points for improvement. All the comments solely pertain to the methodology used. We believe the comments indeed compel us to clarify and/or justify this paper on some issues. However, we disagree with the referee on the statement that our approach signals “severe methodological flaws that undermine their conclusions”. In the following we address the referee’s concerns by indicating where we have made the necessary changes and, in case of disagreement, by providing the arguments on which we have based our choices.

Comment 1: There is no definition of what the authors define as "norms" and "principles" which would have helped us understand what they looked for in the sources they used, and in what way this distinction is relevant for policy.

Authors’ response: We have included a definition of “principles” and “norms” (page 4). We have also added an explanation for how principles and norms relate to governance and why they are important. In the Discussion section we now mention that we acknowledge that the literature and
guidelines may have used the terms differently, but that the reviewed sources are nonetheless informative to establishing a governance framework for data sharing (pages 18 and 19).

Comment 2: The authors claim "systematicity" in their search but this is not sustained by what they present as their search methods. This applies mostly to the selection of guidelines. (It is indeed difficult to systematically identify policy guidelines, but then either avoid a systematic review, or develop a systematic approach.)

Authors’ response: We have meticulously followed the PRISMA checklist for the search, selection and—to the extent possible—data extraction of scientific, peer-reviewed papers. The PRISMA statement, however, does not provide any meaningful guidance for the search, selection and analysis of “grey literature”, such as ethical guidelines—as the referee correctly points out.

We would like to emphasize that though the use of systematic review methodology (in accordance with the PRISMA statement) greatly increases the validity and reproducibility of systematic reviews and meta-analyses of empirical studies, there are limits to which it logically makes sense to adhere to these reporting guidelines for reviews of sources of non-empirical nature. Most importantly, we do not believe that a search strategy demonstrative of more “systematicity” would have made any significant difference in the results. We reasoned that if you consulted a group of international academic and industry experts in the field of health law, regulatory science and research ethics you would end up with the most relevant guidelines for policy and practice. If the reviewer feels that we have left out any guideline of crucial importance for the European community of health data science, we would be more than willing to include an analysis of this guideline in the paper.

With respect to the referee’s final point (“avoid a systematic review, or develop a systematic approach”), we mark this a point of semantics. What do we mean when we talk about a ‘systematic review’? There are many ways to convince your readers that your review is reproducible as long as you describe your approach systematically. Then by definition, every systematic review uses a systematic approach. Obviously, standardized reporting guidelines help us better judge and compare the findings of systematic reviews and meta-analyses of empirical experiments/studies, hence the PRISMA checklist. We can only assume that the referee equates a ‘systematic review’ to a ‘systematic review in accordance with the PRISMA statement’. But the referee’s comments pertain to our review of guidelines, and we have already argued that the
PRISMA checklist is of no added value here. We have described our approach and performed data extraction exactly as we did for the peer-reviewed literature. In our view, that is as systemic an approach as reasonably attainable.

Comment 2.1 The use of Google Scholar - which is not a static database - warrants further explanation (how did the author delimited their search?) in order to claim systematicity?

Authors’ response: The referee correctly points out that Google Scholar is different in nature from the more “typical databases” used to systematically search for scientific, peer-reviewed literature. Yet it is exactly this nature of Google Scholar (GS)—with its continuously updated feed of a broad variety of new sources including grey literature—that we resorted to GS as a fourth database to search. Quoting from Neal Haddaway and colleagues that GS “forms a powerful addition to other traditional search methods” as GS “can find much grey literature and specific, known studies”. The only caveat is that GS should not be used on its own for systematic review searches. In the past, BMC Medical Ethics has accepted papers presenting results from systematic searches in GS. The search in GS was limited as follows (See also Appendix I):

“allintitle: health OR framework OR governance OR recommendations "data sharing" [limit 2006-2017]”

We are not saying this is the only way to conduct a GS search for our research question. But at least it is reproducible. Inclusion and exclusion criteria were applied as for other databases. However, we think other readers may have similar concerns to the one the referee raises. That is why we believe an extra sentence is warranted that describes the rationale for searching in GS (now added to page 4).

Comment 2.2 "National and EU laws and regulations were excluded from this study because we were primarily interested in elements of a governance framework that provides comprehensive moral guidance, not only enforces legal compliance." And yet laws and regulation are expected to be developed on the grounds of moral principles and norms, so this is not adequate justification for excluding them.
Authors’ response: National and EU law are a given to all involved in health data research in the EU. We will have to work with the GDPR no matter what. A lot will depend on the way the GDPR is implemented the different EU Member States. Hence the call for complementary ethical guidance for health data sharing that accompanies legislation.

So, under the assumption that legislation is not sufficient for promoting ethically desirable behavior in the rapidly changing realm of health data science, we believe the choice to limit our analysis to literature and ethical guidelines is a justified one. However, to avoid confusion regarding this point we have taken out the word “regulations” from the text (page 5).

Comment 2.4 "Relevant guidelines and policy documents on data sharing in international health research were identified with help from academic and industry consortium partners with expertise in health law, regulatory science and research ethics." This is not sufficiently descriptive, who were the partners? Why these partners and not some others? Why this method? How are the authors confident that they have not left out important guidelines? The consultation process with experts in itself is not described.

Authors’ response: Partners were identified within the IMI BigData@Heart consortium and selected based on their experience. We have now explicitly mentioned IMI BigData@Heart as well as the numbers of experts in the manuscript text (page 4). As we have already explained in our response to Comment 2, we argue that a group consultation of international academic and industry experts in the field of health law, regulatory science and research ethics gives you a high probability of ending up with a workable number of the most relevant guidelines for policy and practice. We have added this clarification to the Methods and Discussion sections (pages 4 and 18). We made no claim to come an exhaustive or comprehensive list of guidelines (which we even doubt would be possible).

In lines 427-432 we acknowledge the possibility that a relevant guideline might have been overlooked. However, at least so far we have not come across any documents that should have been added. Again, if the reviewer feels that we have left out any “important” guideline that would alter our results substantially (i.e., to conclude our findings do not represent reality), we would be more than willing to include an analysis of this guideline in the paper.
Comment 2.5 Inclusion criteria are poorly described and, based on what the reader can understand, are not appropriate: how can one judge the 'purpose' of a publication (line 93) and what does 'preferably' mean (line 94)?

Authors’ response: We have edited the Methods section substantially to improve readability and understanding. We have added a table in which the inclusion and exclusion criteria are presented more clearly (Table 1 in revised submission). What we mean by papers that were “developed with the purpose to inform policy decision-making” are papers that discuss norms and principles along with tangible measures to facilitate implementation in policy. This phrasing was deliberately used to contrast papers that provided more high-level, and thus more abstract norms and principles without any explicit bridging to implementation in policy. We agree with the referee that the wording could be changed to avoid confusion. We have rewritten these sentences on pages 4 and 5.

Comment 2.6 Why were sources discussing benefits, imperatives and challenges (line 97) excluded? If the authors are looking for ethical principles and norms, such sources could have been relevant.

Authors’ response: In the original submission it says: “Publications that were limited to a discussion of benefits, imperatives or challenges for health data sharing or IT infrastructures for Big Data research were deemed not relevant to the purpose of this review.” Many papers looked promising in initial stages of searching, but later appeared to not meet our inclusion criteria (most notably, no coherent set of norms and principles). You could argue there was no need for this exclusion criterion, but it did help us in the selection process to constantly ask ourselves: Is the central focus of this paper governance, norms and principles OR only the benefits, imperatives or challenges of health data sharing? The inclusion of papers that referred to an ethical principle once or twice simply to make an argument about, for example, why we should be sharing data more broadly would dramatically blow up the number of included sources, without any meaningful gain.

Comment 2.7 "For inclusion, publications were required to present a coherent set of principles and/or norms that could potentially function as or at least be construed as part of a model or framework for responsible data sharing. Documents were included if the content was developed with the purpose to inform policy decision-making and preferably by or in collaboration with
Are these criteria connected by an "and" or an "or"?

Authors’ response: The criteria are connected by “and” (we refer to Appendix 1 and 2 for a breakdown of search terms and the search syntax).

Comment 2.8: “Documents were included if the content was developed with the purpose to inform policy decision-making”. The fact that the authors intended for their work to impact on policy tells us very little about whether any policy was impacted by them. It seems very arbitrary to use this criterion if the objective of the study is to show which principles and norms have been used in actual guidelines.

Authors’ response: “The fact that the [reviewed] authors intended for their work to impact on policy tells us very little about whether any policy was impacted by them”. True—intentions do not necessarily reflect outcomes. But then again, there are no outcomes yet because so far there exists “no blueprint of a broadly accepted governance framework” (Introduction, page 3). That’s exactly why we delve into people’s ideas of what, from an ethical perspective, are important building blocks for an actual governance framework. We also refer to our response to Comment 2.5 in terms of the changed wording.