Author’s response to reviews

Title: Critical Review of the TransCelerate Template for Clinical Study Reports (CSRs) and Publication of Version 2 of the CORE Reference (Clarity and Openness in Reporting: E3-based) Terminology Table

Authors:
Samina Hamilton (sam@samhamiltonmwservices.co.uk)
Aaron Bernstein (Aaron@aaronbernsteinconsulting.com)
Graham Blakey (graham@consult2deliver.co.uk)
Vivien Fagan (vivien.fagan@iqvia.com)
Tracy Farrow (tracy.farrow@ppdi.com)
Debbie Jordon (mail@debbiejordan.co.uk)
Walther Seiler (walther.seiler@bayer.com)
Art Gertel (medscicom@rcn.com)

Version: 1 Date: 03 Jul 2019

Author’s response to reviews:

Dear Mrs Fagan,

Thank you for submitting your manuscript to our journal. I enjoyed reading it. Below you will find comments of individual reviewers I encourage you to address.

Additionally, I would like you to do the following:

1. Change the title and the abstract so it includes the information about the version 2 of the table (e.g. Review of the TransCelerate template for clinical study reports and publication of version 2 of CORE Reference Terminology Table).

Authors’ Response: The title change as suggested is made, but with addition of the word ‘Critical’ at the beginning. The ‘Abstract’ already includes the V2 Terminology Table information in the ‘Results’ part; it is now additionally included in the ‘Methods’ part of the Abstract, with addition of new text: “We also re-examined and edited the Version 1 CORE Reference Terminology Table that we first
published in 2016, and we present this as Version 2 in this communication.”

2. Please delete the appendix and put all the minor suggestions below the major suggestions, (e.g. in the second row of the table, have Headings – then major and minor suggestions sections below as subsections – and do this for all sections, for those without comments, say: None)
Authors’ Response: Subsequent to the above instruction, the following solution for presentation of in-text Table 1 and end of text PDF Appendix 1 was agreed between Mario Malicki (MM), Editor-in-Chief, and authors Sam Hamilton (SH) and Art Gertel (AG) at a teleconference on 17 June 2019:
Only include major PDF Appendix 1 comments in in-text Table 1. In the Legend of Table 1 and in text (in Methods section) state that minor comments and suggestions for all sections of the CSR template are available in PDF Appendix 1. In PDF Appendix 1- which RIPR agree to publish - include a new page at the beginning of the document. This page includes a key to colour coding; contains notes that major comments are included in manuscript Table 1; and ease of navigation, includes a navigational table of contents - with links to the beginning of each individual PDF Appendix 1 section. NOTE: PDF Appendix 1 - which was a Word document in the original submission - has been converted to a fully functional PDF.

3. Delete all descriptions from the CRS template in your table – only list major and minor suggestions.
Authors’ Response: Refer to the agreed solution above.

4. Please justify the need to include the consortium in the author list – as the authors contributions are very detailed, so the rest of the working group (if there is anyone in it not in the authors list. does not seem to merit authorship – or specify the role of the consortium in drafting the table 2 and making comments)
Authors’ Response: There are no other BWG members besides the authors. There are no further roles to specify, so the text ‘…for the Budapest Working group’ at the end of the authors list is changed to ‘(the Budapest Working Group [BWG])’. We believe that the added parenthetic text is the clearest way to show who the BWG are, and this is important as we refer to the BWG often in the paper.

My hope is that you will take the reviewers and my comments as benign and enthusiastic suggestions and requirements of those working in this field who wish to see it grow and improved, even if some of them are written more strictly or harshly, so that your resubmitted version is soon published in our journal.
Authors’ Response: Thank you for the reviewers’ comments. You state that these are ‘…suggestions and requirements of those working in this field [sic]’. However, some of the reviewers' comments reveal a lack of familiarity regarding the reporting of clinical trial results in support of marketing applications for new medicines. Explanations are provided below to support their understanding of our discipline, where necessary.

Please do include a point-by-point response within the 'Response to Reviewers' box in the submission system and highlight (with ‘tracked changes’/coloured/underlines/highlighted text) all changes made when revising the manuscript. Please ensure you describe additional experiments that were carried out and include a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Submission Guidelines on the journal homepage.
Authors’ Response: Detailed replies are included for reviewer comments below. However, there are no ‘additional experiments’ because this is a critical review and appraisal exercise conducted by the authors of this paper on a third-party document.
The due date for submitting the revised version of your article is 09 Jul 2019.

I look forward to receiving your revised manuscript soon.

Best wishes,

Mario Malicki
Research Integrity and Peer Review
https://researchintegrityjournal.biomedcentral.com/

Reviewer reports:

Reviewer #1: The authors report the process to update the CSRs by the CORE developers. It is reported in a perfect and transparent manner, that deserves publication -- at least for me, a non-native English speaker. Authors’ Response: Thank you. I provide 4 minor comments for the consideration of the Authors. Please consider adding a comment in your discussion about your plans to disseminate CSRs. Authors’ Response: In our field, CSRs are not disseminated by their authors, but rather by drugs regulators in the EU and Canada (at the present time). CSR authors have to write the CSRs that regulators disseminate. I have included new text in the Discussion (starting mid paragraph 2) to explain this: “This is particularly important because CSRs are now publicly disclosed by the medicines regulators in the EU [3, 4] and Canada [7], and special care is therefore needed when writing CSRs to balance text and data presentations so that on one hand, the identity of individuals is protected, and on the other hand, data utility is optimised to support medicines regulators in unimpeded assessment of license applications [4]. Direct links in the CSR template to resources that support the writer in this endeavour are therefore essential.”

As I see them, the difference between the primary and the secondary endpoint is that the primary one(s) serves to arrive at a decision under the Neyman-Pearson paradigm (i.e. trial results recommend allowing public access to the intervention in a pivotal trial); and the secondary ones serve to learn more under the Fisher's evidence framework, adapted to CIs philosophy. So, I'm confused because you added a third class of end-points, exploratory. Please, consider, either to simplify, or justify this classification, or providing references Personalized Medicine may help to argue against evidence medicine. A student of mine recently advocates a clearer report for CT (Cortés et al). Please, consider commenting on the convenience, or not, to place the trial within the context of personalized medicine. I.e., to clearly state if the hypothesized effect was or not a constant; or if the report looked at this assumption. Authors’ Response: This paper is about the tools available to help those who write clinical study reports for interventional clinical studies. There are well-established frameworks within the clinical trials industry for reporting trial results, and these frameworks are predicated on industry guidance documents that are enshrined in law. See https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. This page houses all of the ICH efficacy guidelines for the design, conduct and reporting of clinical trials for your interest. Now I will justify ‘exploratory endpoints’. These are a recognised class of endpoints in clinical trials – and are embedded through the entire raft of ICH guidelines (see the guidelines link above). Exploratory
endpoints are commonly designed into earlier phase trials to allow assessment of endpoints that could be further developed in later phase trials if they show promise early on in a drug’s development. This is what we mean by ‘exploratory endpoints’; the context in which we refer to these in the paper is entirely appropriate. Whilst the Cortés paper may be interesting, the rules are clear for interventional clinical trial design and reporting.

Finally, I wonder if the part corresponding to estimands is as 'mature' as the rest of table 2. Unfortunately, I'm not an expert. So, I just suggest that authors double check the wording with experts.

Authors’ Response: The wording was developed with the help of a statistical expert working with author Walther Seiler, named in the ‘Acknowledgements’ section.

Further, we are limited to the example we originally presented in CORE Reference Terminology Table V1: ‘Demonstration of anti-hypertensive efficacy of Test Product’. Company training on estimand is becoming more widespread in our industry and this further confirms our belief that the relevant points have been covered (see info-graphic). We cannot supplement the text any further as it would then not make sense as it would out of context with the objective/endpoints used for our original example.

Reviewer #2: Overall

This manuscript is hard to read and understand. The objectives are not clear, and they seem to change all the way from the abstract to the conclusions section. The reader cannot understand what the aims are, what is the study design, what the authors did and what results they got, the reader can only infer some of it by navigating through confusing text and more confusing tables. Tables are not clear, and unfortunately, we end the reading without knowing what this paper adds to the literature.

Authors’ Response: In some places, clarifications have been added to the text in the paper to more effectively lead the reader through the paper – thank you for those helpful suggestions. In other places, I have added ‘Authors’ Responses’ below which I hope will aid your understanding.

Title

The term "review" is not precise in the title. The title does not make it very clear if the paper is a critical review of a published template or if it adds a literature review. The “by the developers” part of the title does not make clear if the developers did the review (and why to cite this in the title?) or if they built the template (and, again, why mention here?).

Authors’ Response: We accept that the title may have been confusing. The title is adapted as Dr Malicki suggested and additionally includes the term ‘Critical’ so our title is now “Critical Review of the TransCelerate Template for Clinical Study Reports (CSRs) and Publication of Version 2 of the CORE Reference (Clarity and Openness in Reporting: E3-based) Terminology Table”.

Abstract

1) The abstract needs improvements for clarity. The reader cannot have a clear or complete idea of what they are going to find in the full text by reading the abstract as it is now. The reader cannot understand what are the aims of the manuscript by reading the abstract.

Authors’ Response: The Abstract text has been improved, with specific details of changes described below.

2) In the background section, it is not clear what "requires minimum redaction and modification": the
The sentence "Although independent…" is also not clear and useful. The Background could begin with the definition of CORE ("CORE is a complete…") and end in "development". Or the authors could explain better why the aims of CORE are important here.

Authors’ Response:
The point of the sentence "Although independent…" is because we wish to make the point that the two different groups who have produced two different resources are not in competition, but rather are both aiming for a ‘common good’. To make this clearer, we start the Background with the definition of CORE Reference as you suggest. Further text is added to clarify that CORE Reference was “(released May 2016 through a joint endeavour of the European Medical Writers Association [EMWA] and the American Medical Writers Association [AMWA])”. This paragraph has also had text added to show the important difference between CORE Reference and the TransCelerate template as follows: “CORE Reference is a content guidance resource and is not a CSR template”. In the next paragraph, clarification is added that TransCelerate is ‘an alliance of biopharmaceutical companies’. The final statement about CORE Reference and TransCelerate projects serving similar aims is deleted from the Abstract; it is included later in the paper so the idea itself is not lost from the paper.

4) In the Methods section of the abstract, you declare that the CORE authors reviewed the template. However, you did not tell your readers first that you developed the template (when and how, and maybe why). There is no chronological sequence.

Authors’ Response: This is a misunderstanding. We did not develop the TransCelerate CSR template. TransCelerate developed it. We critique their third-party template that was built using our guidance, but that we were not involved with. We had already stated in the Background section a few lines above that TransCelerate released its first version of a CSR template in November 2018. The text for the Abstract Methods section clarifies what exactly we did, and reads as follows:

“The regulatory medical writing and statistical professionals who developed CORE Reference conducted a critical review of the TransCelerate CSR Template. We summarise our major findings and recommendations in this communication. We also re-examined and edited the Version 1 CORE Reference Terminology Table that we first published in 2016, and we present this as Version 2 in this communication.”

5) In the Results section, what are "template findings"? It is tough to get an idea of what you are presenting in the Results section of the paper, according to this description. What did the study find? What were the results?

Authors’ Response: In the ‘Results’ part of the ‘Abstract’ we now state the following: “Our major critical review findings indicate that opportunities remain to refine the CSR template structure and instructional text, enhance content clarity, add web links to referenced guidance documents, improve transparency to support the broad readership of CSRs, and develop supporting resources.

The CORE Reference ‘Terminology Table’ Version 2 includes estimand as a defined term and an
adaptation of the original ‘worked study example’ to incorporate the recently evolved concept of “estimands”.

6) In the Conclusions section, the authors state that the publication intends to do something. Such a comment is not proper to a Conclusions section, but rather to the Objectives/Aims section.
I also don't see how a template can allow "common interpretations”.
Authors’ Response: text is adjusted to: “This publication helps CSR authors to appreciate similarities and differences of two independent resources, and to consider shared interpretations when authoring CSRs. TransCelerate’s CSR template is a unified industry development, built using existing sources including ICH E3 and CORE Reference, and is an important milestone”.
I believe "warmly welcome" is an expression not supported by anything else in the abstract text, because the reader, at this point, did not understand why do we need a template, what it is built for, and why it is innovative or useful.
Authors’ Response: As indicated above, the text is edited to “TransCelerate’s CSR template is a unified industry development, built using existing sources including ICH E3 and CORE Reference, and is an important milestone.”

7) The last section of the abstract highlights so many limitations of the template that the reader is hardly convinced to read further.
Authors’ Response: The reason for writing our paper is to critique a third-party CSR template and say how it could be improved, because it has limitations it its current form.

8) The authors state that the CORE Reference is registered on the EQUATOR website. OK, but it seems, by reading the abstract, that the paper is not about CORE, but about a new template. Was the template registered anywhere? Please clarify.
Authors’ Response: This paper describes a critical review of the TransCelerate CSR template using CORE Reference, so we believe it is most transparent to include registration details for both. The TransCelerate template is only housed on TransCelerate’s own web pages, and is not – to our knowledge – registered elsewhere. So we retain the registration details for CORE Reference and clarify the position as we understand it for the TransCelerate CSR template, with the text addition: “The TransCelerate CSR template is not registered with any external organisation to the knowledge of the authors of this paper.”

9) We suggest that the authors use reporting guidelines to plan and write their abstract. The STROBE Statement is a basic start.
Authors’ Response: We are familiar with the STROBE statement: https://www.strobe-statement.org/index.php?id=strobe-home because we use this to report observational studies. This paper however is not about an observational study, but is rather a critical review – so STROBE is not relevant.

Introduction

1) The Introduction section draws a nice historical description of the CSR scenario, up to line 120. Then suddenly the authors present "a first version of CSR template" by something called TransCelerate… something that the reader is not familiar with at this point of the text. There is no introduction or presentation of what TransCelerate is (an organisation? A document?), why it was created and when. All we can learn is that in November 2018 a template was released, but we have no clue about how it began. So, the history goes well until line 120. From that point on… the reader gets lost.
Authors’ Response: We believe that you refer to the ‘Background’ Section (not the Introduction, as you have stated above). Text is added before the sentence ‘In November 2018...’ which reads: ‘TransCelerate is an alliance among some of the world’s prominent biopharmaceutical organizations with the tagline “accelerating the development of new medicines”. TransCelerate provide solutions that “…are developed collaboratively and can be voluntarily adopted by stakeholders in the clinical research ecosystem” (https://transceleratebiopharmainc.com).’

2) In line 127, the authors state that the CORE Reference had 18K downloads "at the date of publication of this paper". The authors do not know if this paper will be accepted, nor when it will be published. Therefore, the sentence must be changed to "at the date of the writing of this paper". The authors should also comment on why they think 18K downloads mean "global recognition" (did the visitors come from all parts of the world?).
Authors’ Response: There was an editorial comment included in our submitted paper stating that we would update the number of downloads at the time of publication of the paper, but this comment was obviously deleted by the journal editors in the version of the paper that you reviewed.
Text changed to: ‘CORE Reference is a broadly recognised resource as evidenced by 20 000+ downloads by June 2019, and adoption and use testimonials originating from Europe, the USA, Asia Pacific, and Africa (https://www.core-reference.org/adoption-and-use/). TransCelerate recognises CORE Reference as one of two principal sources used in its CSR template development.’

3) At the end of the Introduction, the authors should make it clear:
   a) what is the aim of this paper;
   b) who created the template;
   c) who reviewed it.
Authors’ Response: This text was substantially already in place, but it has been revised so that it is clearer. Text now reads: “The aim of this paper was for the BWG - the developer of CORE Reference – to conduct a critical review of a CSR template that was developed by TransCelerate. TransCelerate used CORE Reference to develop their CSR Template, but did not involve the BWG in its development. We, the BWG, have conducted a thorough critical review and analysis of the TransCelerate CSR Template over the period 11 January to 28 March 2019 and summarise our major findings here to expand on our initial observations on the TransCelerate CSR Template, which we published in a Press Release in December 2018 [11]. We also take this opportunity to review and update the original Version 1 CORE Reference ‘Terminology Table’ and present Version 2, which includes estimand as a defined term and an adaptation of the original ‘worked study example’ to incorporate the recently evolved concept of “estimands”.”

It seems that the information is currently presented in a disorganised, not chronological way. Maybe, the authors could develop using this sequence, if it is right:
   i. Someone (who?) developed a template based on previous work from the BWG (the CORE) ii. The BWG reviewed the template (how? Critically? Delphi involved?) iii. The aim of this paper is to present…. (what? The critical review? The template reviewed?).
The authors should make sure that readers can understand what this paper is about, at this point of the Introduction, without the need of reading the whole methods section. What is the question this paper tries to answer?
Authors’ Response: We have clarified all this as explained above.

Methods

1) I don't understand why the methods section should begin with the (incomplete) description of a
review team — even before the reader is told this is a review paper. The Methods section should start with a declaration of the study design: a narrative review? A critical evaluation of a "template"? A systematic review? An observational study? What is it?

Authors’ Response: Deleted entire paragraph about composition of the BWG, and we now state our methods as follows: “The BWG discussed similarities and differences between the TransCelerate CSR Template and CORE Reference. The BWG’s comments on the TransCelerate CSR Template were collated and proof-checked, and the resulting unabridged critical review comments are provided in PDF Appendix 1. We classified a proportion of the review comments as major findings. In Table 1, we summarise these, and we make recommendations on enhancements that may be applied to the TransCelerate CSR Template with respect to each major finding. Finally, this manuscript was drafted, and underwent review by the BWG.”

2) The second block of the Methods section (lines 153-159) state that "the team reviewed the TransCelerate template. But again: what is the template reviewed? Where? When was it created?

Authors’ Response: Text above addresses this point.

3) There seems to be a mixture of results and methods in the Methods section. We suggest that the authors critically review this. Outputs (from line 153 to 166) are probably results, not methods.

Authors’ Response: We have better separated the methods and results to address this point.

3) The authors do not describe (and they should) in the Methods section:
- what were the techniques to build the template and to review it
  Authors’ Response: We did not build the template, TransCelerate did, so we have no working knowledge of how they built it. We state that we (BWG) performed a critical review.
- what were the tools used (for instance, software)
  Authors’ Response: We did not use any tools for critical review; we describe our process (see below).
- who did the evaluations and how (there is some mention of "statistics" in the "team" block above, but what statistical analysis was undertaken?)
  Authors’ Response: We did not perform any statistical analysis because this was not relevant in our review; our Statistician critically reviewed the CSR Template; we describe our process (see below).
- when these evaluations happened and where
  Authors’ Response: Dates added.

Text has been edited in the final paragraph of the ‘Background’ section: “We, the BWG, have conducted a thorough critical review and analysis of the TransCelerate CSR Template over the period 11 January to 28 March 2019 and summarise our major findings here to expand on our initial observations on the TransCelerate CSR Template, which we published in a Press Release in December 2018 [11]. We also take this opportunity to review and update the original Version 1 CORE Reference ‘Terminology Table’ and present Version 2, which includes estimand as a defined term and an adaptation of the original ‘worked study example’ to incorporate the recently evolved concept of “estimands”.”

4) There is no declaration of ethics approval or waiver anywhere in the Methods section, where it would be appropriate.

Authors’ Response: Not relevant because this is not an endeavour requiring ethics approval or a waiver. It is a critical review exercise on a published resource.

Results
1) Are the authors sure that the journal prints in colour (so that they can "pink highlight" something)?
Authors’ Response: References to pink highlighting are now deleted from the text of the paper. These are included in the PDF Appendix 1. It has been confirmed by the journal editor that the colour-coding is appropriate in PDF Appendix 1 and will show up.

2) "Word file" is entirely unnecessary in the results section (line 170). "Text file" is enough. The journal reader will probably not be able to see "formatting marks" or "hidden text" either (line 175). The authors should write their paper in the format that it would appear in the published version of the RIPR journal.
Authors’ Response: The original Word file has now been converted to a fully functional PDF, so references to formatting marks are deleted consistently from the paper.

3) The authors mention "these are our key recommendations for consideration in further development of the template"... Well, from the "developing a template" and "reviewing a template" sentences, now the reader begins to think that the manuscript's objective was to build recommendations....!
Authors’ Response: We include explanation that we provide recommendations in all sections of the paper.

4) I could not understand Table 1. I could not get what it is presenting, what are the "page numbers" in the second column and would probably understand it better if the authors explained the basis for it (i.e., what they are criticising) in the text and/or in the Table title. I could not find anything marked in pink as they stated - and marking in pink might not be a good idea considering the journal graphic style.
Authors’ Response: PDF Appendix 1 included the pink highlights. Table 1 has been revised to address possible interpretational issues; Appendix 1 is now a PDF and the pink colour-coding is described therein.

5) Table 2 seems to have been already published elsewhere. Do the authors have permission for reproduction? Also: is this what Table 1 was criticising? (question above)
Authors’ Response: We, the BWG published the original Terminology Table as part of open-access CORE Reference Version 1. So we allow ourselves the permission to use our own Table in this paper. Table 1 is critiquing PDF Appendix 1 as already stated multiple times in the paper and in the responses to these questions.

6) Page 33 of this pdf shows a "confidential" table with a lot of comments. I do not think this is proper for publication. And I do not believe the reader should be made to go through all these comments to understand what the authors are talking about. The authors should synthesise these results someway. The readers should not be made to read your lab diary.
Authors’ Response: This is PDF Appendix 1 – i.e. TransCelerate’s CSR template. The comments are our critique of it – i.e. the entire point of this paper. The word ‘confidential’ appears because it is part of the TransCelerate CSR Template – which they intend for use by pharmaceutical companies and others who author CSRs. For this reason, they have included the word ‘confidential’. Its inclusion is entirely appropriate considering the expected utility of the template. The reader can read the major (critical review) comments in Table 1 of our paper; if they wish to see all comments in situ, they can review PDF Appendix 1. The inclusion of an Appendix to a publication is commonplace, in our experience.
Discussion

1) In the first line of the Discussion section, TransCelerate is described as an alliance. Not a template for writing, as suggested in the other sections of the paper. This highlights the need for adequately presenting what you are doing in a logical, chronological, and clear way to your reader, especially regarding aims and methods.
Authors’ Response: Because we now state what TransCelerate is earlier in the paper, we have deleted this entire paragraph from the Discussion.

2) The authors wrote the whole Discussion section citing only one reference (no. 12). This is odd. The purpose of a discussion section is to comment and argue one’s results with those from others. There are many sentences in the Discussion section that lack supporting and therefore look opinative.
Authors’ Response: Parts of the Discussion are our opinion – because we interpret our critical review findings. This seems appropriate. In other places the citations have been added.
Also, from lines 196 to 199, and again 245 to 247, the authors use quotation marks for sentences, suggesting that they took those sentences from a text published elsewhere. But where? Please, cite references!
Authors’ Response: The first set of quotation marks indicate text from the TransCelerate website. This text is relocated to earlier in the paper and the web address has been included in parentheses. The second set of quotation marks clearly relate to text on page 6 of CORE Reference, as stated.

3) "The BWG views the TransCelerate CSR template endeavour as a valuable addition…” (line 202). This seems to be the opinion of BWG. Was this published/endorsed by BWG? Is this a result of your study? (if so, please report it in the Results section).
Authors’ Response: This is our opinion and is first published in this paper. It is not a Result.

4) Lines 210 to 211 cite something as "Level 1" and "Level 2", but the reader, at this point of the text, may have no idea about what it is. The whole paragraph from line 207 to 215 is unclear.
Authors’ Response: Text adapted to: “This is currently lacking due to the TransCelerate CSR template red instructional text (which shown in PDF Appendix 1) to not rearrange or reorder Level 1, Level 2 and lower hierarchy headings.”

5) The authors jump from discussing the availability of their template, from lines 217 to 235, to "primary and secondary endpoints" in the next paragraph, starting on line 237, without any linkage between the two. It is an abrupt, unjustified change of subject. The same applies to the jumping from this paragraph to the one starting on line 254. Indeed, there is little or no connection between paragraphs in this paper, which reduces readability.
Authors’ Response: Text added to end of Discussion paragraph 2 tells the reader what we will discuss before we discuss it – and this helps the flow:
“There are however, differences, which broadly fit into the themes discussed below, and include transparency and public disclosure; structural flexibility; section-to-section continuity; sectional numbering; and instructional text completeness and clarity.”
Note that the transparency and public disclosure theme is now relocated to appear first in the topics in the Discussion. This also improves the flow.

6) The paragraph starting on line 237 is difficult to understand. The authors seem to require the reader to have gone through additional material to know what they are talking about.
Authors’ Response: This refers to where assets are placed on TransCelerate’s website. The reader can believe that the material is located there because we tell them it is. There is no need for them to go
through it, merely to know where it is located.

7) The paragraph starting on line 276 seems to be a critic of the TransCelerate template. Is that it? What is the connection between this and the other paragraphs?
Authors’ Response: This statement is placed logically in the Discussion and is after the actual template critique Discussion. It shows that TransCelerate did not disclose Stakeholders in its CSR Template development; CORE Reference did.

Conclusions

In the Conclusion section, the reader is presented with a new, different, aim of the paper: to differentiate between CORE Reference and the TransCelerate. Some problems:
1) this had not been done before in the article, and if it is true, this should be pasted into the Objectives section in the Introduction;
2) the conclusion is usually not the right place to declare aims;
3) the results of this paper did not present such differences;
4) the methods as described in this paper did not show how the authors would detect and explain the differences;
5) the authors state that they have shown that the application of CORE provides additional instructional value for users of the template. I am sorry, but they did not. They did not show anything like that throughout the paper.
Authors’ Response: Statement edited in Conclusion to ‘Application of CORE Reference in CSR authoring…’ i.e. remove the word ‘show’. We believe that this solves points 1 though 5 above.
6) Again, the "warmly welcomed" expression might be out of place. Authors’ Response: Agree, removed.

In the declarations section, the authors state that the TransCelerate has already been disseminated to the press, by a press release. The editors should think about originality and embargo issues. Also, it seems that authors are republishing original material published elsewhere (Table 2).
Authors’ Response: We, the BWG, created both the Press Release, and CORE Reference Terminology Table (adapted in Table 2) and published them open access. We allow ourselves to use this material so that we can write this paper. There is no embargo. We clearly state all this in the ‘Declarations’ section of this paper; the BWG is added as the authors of both to make it clearer.

References

The references are not cited properly, especially in the discussion section.

Authors’ Response: Use of citations is increased in the Discussion (see above).

Reviewer #3: The TransCelerate CPT team welcomes the helpful feedback from the authors and will look to revising the existing assets and template to incorporate some of the suggestions. The template was based on the core principles in ICH E3 and direct experience by member company interactions with Regulatory Authorities as well as the CORE Reference by the Budapest Working Group. And as such the template represents a synthesis of the best practices. Updates are refreshed regularly. Further
feedback is welcomed from all users of the CPT suite of templates and can be provided via the following link: https://www.transceleratebiopharmainc.com/assets/common-protocol-template/feedback-form.

Authors’ Response: We note that Reviewer #3 is a member of the TransCelerate CSR Template development team, and that no actual comments on our paper are proferred.

------------------------------------------------------------------------------------------------------------------------

Please also take a moment to check our website at https://www.editorialmanager.com/ripr/l.asp?i=13449&l=2OGZ2VXF for any additional comments that were saved as attachments. Please note that as Research Integrity and Peer Review has a policy of open peer review, you will be able to see the names of the reviewers.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES-HS) and American Journal Experts (http://bit.ly/AJE-HS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources)