PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for A Systematic Scoping Review of Reasons Given to Justify the Performance of Randomized Controlled Trials
AUTHORS	Dewar, Brian; Fedyk, Mark; Jurkovic, Lucas; Chevrier, Stephanie; Rodriguez, Rosendo; Kitto, Simon; Saginur, Raphael; Shamy, Michel

VERSION 1 – REVIEW

REVIEWER	Prof. Dr. Sabine Ruf Justus-Liebig-University of Giessen, Germany
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	The question whether an RCT is necessary or not is a question of utmost importance for the future of research in any medical field. Thus, the present review is of high importance. The information provided suggests, that the review will be confined to medical trials only. It is not clear whether dental trial are included or excluded – the latter should be specified. In the article summary – point 2 is an incomplete sentence – please check! In Material and Methods you state, that the search will be conducted between October 2017 and September 2019. Is this the covered period of literature search? If not, this information should be changed for the years covered by you search.

REVIEWER	Jean Raymond Centre hospitalier de l'Université de Montréal (CHUM) Canada
REVIEW RETURNED	27-Nov-2018

GENERAL COMMENTS	Manuscript ID bmjopen-2018-027575 "Protocol for a Systematic Scoping Review of Reasons Given to Justify the Performance of Randomized Controlled Trials" General comments I have no experience in reviewing a 'protocol for a systematic scoping review'. The proposed subject is extremely important and deserves a review. However, I see a number of important difficulties that I will mention, but they should not be used as reasons to reject the manuscript: 1. I have little confidence that the search strategy will include all or most pertinent articles. Authors should have a list of 'classical' and 'non-classical' articles (a substantial number) on the topic they want to review and verify that their search strategy has succeeded in finding them. An honest report of the result of such an exploration would be appreciated in the final paper.

	2. Authors assume RCTs need justification and this assumption may bias their work. While the assumption that RCTs need justification may be shared by a number or majority of people since the Belmont report, this fact alone must have biased the literature ever since. Once more this bias is not discussed in the present paper but should be discussed in the final paper. 3. Authors seem to conflate randomized allocation, equipoise and RCTs. There are many components to a RCT, and they all carry ethical impacts (selection criteria, choice of treatment alternatives, allocation ratios, extra tests or visits, monitoring, rigid or flexible protocols, funding sources etc…). A RCT may be justified, but not THAT particular RCT. If I understand their manuscript, authors are particularly interested in RCTs because RCTs use randomized allocation, and in equipoise as a condition for randomized allocation (although there are dozens of different concepts of equipoise), or in related concepts such as uncertainty or indifference. If this is the case, I encourage authors to review the manuscript one sentence at a time and re-write the paper keeping that in mind. This comment becomes crucial when the authors claim they are looking for a set of criteria that could be used by regulators and funders. 4. For the same reasons (providing criteria for regulators or funders) I am worried about the spirit and overall purpose of the methodology. If there is no intent to select papers according to quality (and I hardly see how this could fairly be done) or any other principle; if there is no reflection on what is needed for regulators or funders to support or reject a particular RCT; if there is no declared loyalty to a principle guiding the inclusion of various articles (historical importance; exhaustivity; normativity; frequency; standard use; or whatever), on what basis would authors write the results of the review, draw conclusions or recommend criteria? Other comments: 1. Who is the author(s) of the various articles to be included: what to do when there are many authors with various backgrounds? 2. I am always worried about consensus: why not provide an honest report of divergences in interpretations of the data by various readers? Or at least some indication of the difficulties involved?

REVIEWER	Robin Pap Western Sydney University, AUSTRALIA
REVIEW RETURNED	26-Jan-2019

GENERAL COMMENTS	General comments: Thank you for the opportunity to review this manuscript. I thoroughly enjoyed reading the protocol and think it details a novel and well-considered method to answer an important question. The authors aim to search the literature to scope and map the reasons provided to ethically justify performing randomised controlled trials (RCTs). Furthermore, they intend to conduct meta-aggregation of the qualitative data obtained. In doing so, the authors are combining aspects of the methods used in conventional scoping reviews and systematic reviews of qualitative evidence. Overall, the authors have explained and justified this somewhat unconventional but appropriate approach well. Paragraph 3 on page 7 also provides thorough reasons why the authors have chosen not to assess for risk of bias. However, the general purpose and method of scoping reviews (most importantly the

	absence of an assessment of the quality of included studies/literature) and the implication this will have on the evidence synthesised by this review needs to be considered more carefully. It should be made clearer to the reader that the authors understand that what they are conducting is a scoping review with methods adopted from systematic reviews of qualitative evidence, rather than a systematic review of qualitative evidence which neglects to scrutinise the quality of included studies. Especially the paragraph describing some of the planned dissemination and utilisation of the findings in future research aiming to develop a revised ethics framework for clinical trial evaluation (page 8) needs to demonstrate awareness of inherent limitations of scoping reviews. This section refers to the review as a systematic review which is inconsistent. It needs more detail to eliminate any doubt about whether the authors fully understand their applied methods and to what extent this scoping review's output can validly inform the next research phase. The sections titled 'Data Items' (extraction) and 'Data Synthesis' detail outputs of the review. It would be helpful to have a separate paragraph which details the presentation of results. Whilst the PRISMA extension for scoping reviews was published in 2018, no scoping review specific protocol checklist exists. However, it may be useful to complete (where applicable) and attach the PRISMA-P as a supplement. Specific comments: Page 3, line 41: Missing "which" or "that", i.e. "… an ethics problem which has resisted…" Page 3, line 44: This needs rephrasing. This is predominantly a scoping review with methods more routinely utilised in qualitative systematic reviews. Page 4, lines 9-11: The sentence starting with "There are, of course, less obvious …" requires a reference. Page 5, line 16: Consider adding 'ethically' to your objective so that it corresponds accurately with your question in line 29, i.e. "This systematic scoping review explores the reasons given to ethically justify the performance of ..." Page 8, line 18: Change to "systematic scoping review" for consistency and accuracy. See general comments. Page 8, line 29: The abbreviation 'REB' needs initial definition/introduction. Page 8, line 34: Change to "systematic scoping review" for consistency and accuracy. See general comments. Page 8, line 39: It is unclear who MCFS is as it does not correspond to any of the authors initials.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Prof. Dr. Sabine Ruf
Institution and Country: Justus-Liebig-University of Giessen, Germany
Please state any competing interests or state 'None declared': None declared

The question whether an RCT is necessary or not is a question of utmost importance for the future of research in any medical field. Thus, the present review is of high importance. The information provided suggests, that the review will be confined to medical trials only. It is not clear whether dental trials are included or excluded – the latter should be specified.

Thank you for this comment. We have specified that any justification for an RCT regardless of discipline may be included in the first paragraph on page 3.

In the article summary – point 2 is an incomplete sentence – please check!

Thank you for bringing this to our attention. We have appropriately edited the bullet point on page 1.

In Material and Methods you state, that the search will be conducted between October 2017 and September 2019. Is this the covered period of literature search? If not, this information should be changed for the years covered by you search.

Thank you for this question. We meant for this statement to be the time during which we are physically undergoing the review. The covered period of the literature search will be from 1948 through the present, as noted in the 'Setting and Time Frame' section of 'Eligibility Criteria' as well as in the search strategies appendix. We have changed our wording to make this more explicit in the text, in the first paragraph under 'Methods and Analysis'.

Reviewer: 2
Reviewer Name: Jean Raymond
Institution and Country: Centre hospitalier de l'Université de Montréal (CHUM), Canada

Please state any competing interests or state 'None declared': I declare no conflict of interest

General comments
I have no experience in reviewing a 'protocol for a systematic scoping review'. The proposed subject is extremely important and deserves a review. However, I see a number of important difficulties that I will mention, but they should not be used as reasons to reject the manuscript:

1. I have little confidence that the search strategy will include all or most pertinent articles. Authors should have a list of 'classical' and 'non-classical' articles (a substantial number) on the topic they want to review and verify that their search strategy has succeeded in finding them. An honest report of the result of such an exploration would be appreciated in the final paper.

Thank you for this interesting comment. This is a valuable methodological point that we will include in the final paper. Informally, we have ensured that our search has identified well-known and seminal articles. Formally, we will determine the list of important papers via the number of citations in the field and ensure that they have been captured by our search strategies. This has been noted in the 'information sources' section of 'Eligibility Criteria'.

2. Authors assume RCTs need justification and this assumption may bias their work. While the assumption that RCTs need justification may be shared by a number or majority of people since the Belmont report, this fact alone must have biased the literature ever since. Once more this bias is not discussed in the present paper but should be discussed in the final paper.

Thank you for this interesting comment. It is true that there are those who believe that RCTs do not need to be justified. We are confident that our search methodology will capture papers that make this argument. If this argument is not being made in the literature, then we cannot capture it. However, we believe that the notion that RCTs should be justified remains dominant in the discourse, and will be relevant to the stakeholders we wish to reach: regulators, whose job it is to ensure that studies are ethically justified, and funders, who carry ethical responsibilities in their disbursements. Potential sources of bias will be discussed as a weakness in the final paper.

3. Authors seem to conflate randomized allocation, equipoise and RCTs. There are many components to a RCT, and they all carry ethical impacts (selection criteria, choice of treatment alternatives, allocation ratios, extra tests or visits, monitoring, rigid or flexible protocols, funding sources etc…). A RCT may be justified, but not THAT particular RCT. If I understand their manuscript, authors are particularly interested in RCTs because RCTs use randomized allocation, and in equipoise as a condition for randomized allocation (although there are dozens of different concepts of equipoise), or in related concepts such as uncertainty or indifference. If this is the case, I encourage authors to review the manuscript one sentence at a time and re-write the paper keeping that in mind. This comment becomes crucial when the authors claim they are looking for a set of criteria that could be used by regulators and funders.

Thank you for this comment. The reviewer's reading is correct that we are most interested in the justifications provided for randomization in randomized clinical trials. We have clarified this point in our methods and in the manuscript. Equipoise is a justification offered in the literature, but is not synonymous with randomization or with RCTs. We will review our text to ensure that this is explicit.

4. For the same reasons (providing criteria for regulators or funders) I am worried about the spirit and overall purpose of the methodology. If there is no intent to select papers according to quality (and I hardly see how this could fairly be done) or any other principle; if there is no reflection on what is needed for regulators or funders to support or reject a particular RCT; if there is no declared loyalty to a principle guiding the inclusion of various articles (historical importance; exhaustivity; normativity; frequency; standard use; or whatever), on what basis would authors write the results of the review, draw conclusions or recommend criteria?

We thank Dr Raymond for his concerns, and we hope that we will address them in the revised manuscript. Specifically, this review seeks to catalogue the reasons given for randomization in RCTs. It is not designed to provide an assessment of the quality of the paper in which that reason appears, or of the prominence of the author, etc. We recognize this as a potential limitation, but we were not able to arrive at a methodology that would incorporate quality assessment without introducing confounding bias. Similarly, adhering to a particular ideology or principle would, we felt, negatively impact the quality of the work. Like most ethical theorists, we have our own opinions about what should or should not justify RCTs. However, our methodology is designed to limit these personal biases.

Other comments:
1. Who is the author(s) of the various articles to be included: what to do when there are many authors with various backgrounds?

Thank you for bringing this to our attention. We have updated the text to state that when there are multiple authors, the first author's credentials will be captured, as it is assumed that he or she was most responsible for the contents of the work.

2. I am always worried about consensus: why not provide an honest report of divergences in interpretations of the data by various readers? Or at least some indication of the difficulties involved?

Thank you for this excellent suggestion. We have updated the 'Data Items' section of our protocol to discuss how divergencies in interpretations of the data will be addressed in the final paper, as it pertains to both data capture and data coding in the 'Data Collection and Analysis' section.

Reviewer: 3
Reviewer Name: Robin Pap
Institution and Country: Western Sydney University, AUSTRALIA
Please state any competing interests or state 'None declared': None declared

General comments:
Thank you for the opportunity to review this manuscript. I thoroughly enjoyed reading the protocol and think it details a novel and well-considered method to answer an important question. The authors aim to search the literature to scope and map the reasons provided to ethically justify performing randomised controlled trials (RCTs). Furthermore, they intend to conduct meta-aggregation of the qualitative data obtained. In doing so, the authors are combining aspects of the methods used in conventional scoping reviews and systematic reviews of qualitative evidence. Overall, the authors have explained and justified this somewhat unconventional but appropriate approach well. Paragraph 3 on page 7 also provides thorough reasons why the authors have chosen not to assess for risk of bias. However, the general purpose and method of scoping reviews (most importantly the absence of an assessment of the quality of included studies/literature) and the implication this will have on the evidence synthesised by this review needs to be considered more carefully. It should be made clearer to the reader that the authors understand that what they are conducting is a scoping review with methods adopted from systematic reviews of qualitative evidence, rather than a systematic review of qualitative evidence which neglects to scrutinise the quality of included studies. Especially the paragraph describing some of the planned dissemination and utilisation of the findings in future research aiming to develop a revised ethics framework for clinical trial evaluation (page 8) needs to demonstrate awareness of inherent limitations of scoping reviews. This section refers to the review as a systematic review which is inconsistent. It needs more detail to eliminate any doubt about whether the authors fully understand their applied methods and to what extent this scoping review's output can validly inform the next research phase.

Thank you for this excellent comment. We agree that it is best to refer to the paper as a scoping review, and have made this explicit.

The sections titled 'Data Items' (extraction) and 'Data Synthesis' detail outputs of the review. It would be helpful to have a separate paragraph which details the presentation of results.

Thank you. We have added this section.

Whilst the PRISMA extension for scoping reviews was published in 2018, no scoping review specific protocol checklist exists. However, it may be useful to complete (where applicable) and attach the PRISMA-P as a supplement.

Thank you for this comment. We have included the PRISMA checklist.

Specific comments:

Page 3, line 41: Missing “which” or “that”, i.e. “… an ethics problem which has resisted…”

Thank you for bringing this to our attention. It has been addressed.

Page 3, line 44: This needs rephrasing. This is predominantly a scoping review with methods more routinely utilised in qualitative systematic reviews.

Thank you for bringing this to our attention. We have amended the text to reflect this suggestion.

Page 4, lines 9-11: The sentence starting with “There are, of course, less obvious …” requires a reference.

Thank you for bringing this to our attention. We have added appropriate referencing.

Page 5, line 16: Consider adding ‘ethically’ to your objective so that it corresponds accurately with your question in line 29, i.e. “This systematic scoping review explores the reasons given to ethically justify the performance of ...”

Thank you for bringing this to our attention. We have made this amendment.

Page 8, line 18: Change to “systematic scoping review” for consistency and accuracy. See general comments.

Thank you for bringing this to our attention. We have made this change.

Page 8, line 29: The abbreviation ‘REB’ needs initial definition/introduction.

Thank you for bringing this to our attention. We have made this change.

Page 8, line 34: Change to “systematic scoping review” for consistency and accuracy. See general comments.

Thank you for bringing this to our attention. We have made this change.

Page 8, line 39: It is unclear who MCFS is as it does not correspond to any of the authors initials.

Thank you for bringing this to our attention. We have amended MCFS to MS to match Michel Shamy, senior author.

VERSION 2 – REVIEW

REVIEWER	Robin Pap Western Sydney University, Australia
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	Thank you for the opportunity to review this revised manuscript. The authors have made some changes; however, these inadequately address the concerns I raised in my initial review. Specifically (authors page numbers): - Page 1, article summary bullet-point 3: This new sentence does not accurately summarise the methodological approach described in the rest of the manuscript and discredits the methods of scoping reviews. Consider: "We intend to produce a scoping review which in its data analysis will draw upon methods typically associated with qualitative systematic review." In this way, you still state that you are applying a scoping review methodology, it doesn't sound like scoping reviews are less rigorous, and you accurately describe that only the data analysis uses methods routinely employed in systematic reviews of qualitative evidence. - Page 2, line 5: The abbreviation ECMO requires introduction, i.e. extracorporeal membrane oxygenation (ECMO) - Page 2, lines 4-6: I'm not familiar with this controversy, but the sentence states that it occurred in recent years, yet the reference added is from 1989. This does not make sense to me and I anticipate it wouldn't to many of the readers either. Is there a more recent reference that could be used to support this statement about the example of the recent controversy? - Page 7, Ethics and Dissemination: The concerns I raised previously about demonstrating awareness of the inherent limitations of scoping reviews was not adequately addressed. As mentioned then, most importantly the absence of an assessment of the quality of included studies and the implications this will have on the evidence produced by this review needs to be considered more carefully.

VERSION 2 – AUTHOR RESPONSE

Thank you very much for your consideration of this protocol. We will address Mr. Pap's points below.

- Page 1, article summary bullet-point 3: This new sentence does not accurately summarise the methodological approach described in the rest of the manuscript and discredits the methods of scoping reviews. Consider: "We intend to produce a scoping review which in its data analysis will draw upon methods typically associated with qualitative systematic review." In this way, you still state that you are applying a scoping review methodology, it doesn't sound like scoping reviews are less rigorous, and you accurately describe that only the data analysis uses methods routinely employed in systematic reviews of qualitative evidence.

Thank you to Mr. Pap for this thoughtful comment. We have made this change.

- Page 2, line 5: The abbreviation ECMO requires introduction, i.e. extracorporeal membrane oxygenation (ECMO)

Thank you very much for this comment. We have introduced this abbreviation.

- Page 2, lines 4-6: I'm not familiar with this controversy, but the sentence states that it occurred in recent years, yet the reference added is from 1989. This does not make sense to me and I anticipate

it wouldn’t to many of the readers either. Is there a more recent reference that could be used to support this statement about the example of the recent controversy?

Thank you to the reviewer for bringing this to our attention. We have removed 'in recent years' to prevent any confusion.

- Page 7, Ethics and Dissemination: The concerns I raised previously about demonstrating awareness of the inherent limitations of scoping reviews was not adequately addressed. As mentioned then, most importantly the absence of an assessment of the quality of included studies and the implications this will have on the evidence produced by this review needs to be considered more carefully.

Thank you very much for this raising this concern. We are interested in cataloguing the reasons offered for randomization throughout a vast body of literature, not appraising the quality of each individual manuscript, as this is not relevant to the data we are extracting. While we could have sought to assess the quality of each individual reason offered, we felt that this would have imparted unnecessary bias into our analysis. As we are extracting reasons from a large number of different kinds of studies, this heterogeneity makes a standardized quality assessment impracticable. While we could have applied a series of quality assessment tools covering each potential manuscript type, we did not feel that this would add to the relevance of our analysis.