PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a core outcome set in paediatric sepsis in low and middle-income countries
AUTHORS	Wooldridge, Gavin; Murthy, Srinivas; Kissoon, Niranjan

VERSION 1 – REVIEW

REVIEWER	Kirsten Møller Rigshospitalet, Copenhagen, Denmark
REVIEW RETURNED	23-Nov-2019

GENERAL COMMENTS	This manuscript is a protocol for establishing a set of minimum requirements for outcome (a core outcome set) reporting for studies of paediatric sepsis in low-to-middle income countries. A three-step approach is used, i.e., a systematic review of outcomes in the current literature, a two-part Delphi process, and a consensus meeting to establish the final core outcome set. In my opinion, this is a very well-written and concise manuscript. The planned study is from a group with extensive experience in paediatric intensive care and addresses a clinically relevant and interesting topic. The process is generally clearly described, and I have only few comments for the authors. 1. In the abstract, the first sentence consists of two statements, the first of which starts with “Despite”. However, because the two statements are not contradictory, this word is not appropriate here. I suggest rephrasing to, e.g., “Sepsis is a leading cause of death in children worldwide and has recently been declared a major global health issue.” 2. A timeline would be interesting; i.e., when do the authors hope / expect to conduct the different substudies? 3. In contrast to the very clear requirements for an individual outcome to be included and excluded in the outcome set based on ratings and votes, I found it somewhat unclear how the feasibility issues raised at the final consensus meeting will be handled. 4. I struggled a little to understand the precise meaning of “low middle-income countries”. I suggest that the term be slightly altered to “low-to-middle income countries”.

REVIEWER	Paula Williamson University of Liverpool, UK I am an author on the guidance documents have used to review this protocol manuscript.
REVIEW RETURNED	11-Jan-2020

GENERAL COMMENTS	The authors are to be congratulated on their plan to reduce waste in

	research through the development of a core outcome set. I have reviewed this protocol against both the COS-STAD guidance for developing core outcome sets (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002447) and the COS-STAP guidance for a protocol for a core outcome set development study (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3230-x) . The authors only refer to the COS-STAR reporting guideline, so may wish to review their plans against these other two guidance documents which are now well-accepted in this field of research. Abstract (1) The authors say 'rank' when the Methods later suggest 'score'. (2) There is reference to both a two-stage e-Delphi survey and a 3-step Delphi survey - please clarify. Background (3) COS-STAP standard 2a - 'Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation' – more justification about the need for this study should be given. In particular: (a) Please review other published and ongoing studies (reviews and COS) in the area, e.g. from the COMET database: http://www.comet-initiative.org/studies/details/740?result=true http://www.comet-initiative.org/studies/details/1131?result=true http://www.comet-initiative.org/studies/details/1317?result=true http://www.comet-initiative.org/studies/details/104?result=true http://www.comet-initiative.org/studies/details/408?result=true http://www.comet-initiative.org/studies/details/375?result=true (b) What is the rationale for just including stakeholders from LMICs? Why not aim for a globally relevant COS, that includes LMICs? The 'what should be measured' may well be the same, even if the 'how' may differ by income status. Methods (4) Please give the specific link to your study in the COMET database – http://www.comet-initiative.org/studies/details/1400?result=true . (5) Scope statement (a) Please add that this is a COS for clinical trials. (b) COS-STAD standard 4, and COS-STAP 3b, requires the scope to include a statement about which interventions the COS will be applicable to, any or particular types; please add this information. This should then be clearly stated in relation to the eligibility criteria for studies in the systematic review. (6) Systematic review – do the authors intend to register a fuller protocol for this component with PROSPERO? (7) A reference should be provided for the list of low-middle income countries as defined by the World Bank. (8) Reviewing published studies will inevitably mean results are for outcomes chosen by trialists several years ago at the time the studies were being designed. Have the authors considered also including ongoing studies in trials registries? (9) COS-STAD standard 8 requires that the initial list of outcomes to be considered should include patients' views as well as those of health professionals. The systematic review of trials is unlikely to cover the former. How will the authors meet this standard?

	(10) Data extraction and analysis (a) It is usual for there to be some form of validation by a second reviewer, even if only for a sample of studies. (b) How will the outcome categories be chosen? (c) How will the results from the systematic review be analysed? (11) Stakeholders – COS-STAP 4 '…how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study' - more detail is needed about the process for recruiting participants in the Delphi survey. (12) The involvement of patients and their parents or guardians in the Delphi is not clear. The text suggests they will be included through a survey, rather than the Delphi, using a researcher-administered questionnaire. How will ambiguity of language in the questionnaire be avoided (COS-STAD 11)? More detail is required as to how their views will be included in the consensus process, and why they are not participants in the Delphi alongside health professionals and researchers. How many patients and parents or guardians will be included? (13) COS-STAD 9, COS-STAP 8 and 9 – more detail about the analysis of the data is required, including what is meant by 'descriptive statistics'. (14) Consensus definition - Will the results from all participants be pooled before the definition is applied? See comment 12 above. If so, how will the voices of all stakeholder groups be represented fairly? This comment applies to both the Delphi survey and the consensus meeting. (15) Consensus meeting (a) It is not clear whether all stakeholder groups will be represented at the meeting. For example, will parents or guardians be invited? (b) The final sentence suggests there will be some consideration of the 'how' to measure the core outcomes. More details about this stage of development, or the plans for this stage, should be given. The authors may wish to refer to the COSMIN-COMET guidance for this - https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1555-2 .

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1) In the abstract, the first sentence consists of two statements, the first of which starts with "Despite". However, because the two statements are not contradictory, this word is not appropriate here. I suggest rephrasing to, e.g., "Sepsis is a leading cause of death in children worldwide and has recently been declared a major global health issue."
Abstract sentence now reads:
Sepsis is the leading cause of death in children worldwide and has recently been declared a major global health issue.

2) A timeline would be interesting; i.e., when do the authors hope / expect to conduct the different substudies?
Timeline now included in methods section: See in editorial response 3 and 4. Plus have included figure 1.

3) In contrast to the very clear requirements for an individual outcome to be included and excluded in the outcome set based on ratings and votes, I found it somewhat unclear how the feasibility issues

raised at the final consensus meeting will be handled
Now reads:
A formal feasibility matrix will be incorporated to inform this process so as to ensure that feasibility is assessed in a standardized way. Those outcomes that are deemed feasible by ≥70% of panellists, will meet consensus for inclusion into the COS.

4) I struggled a little to understand the precise meaning of “low middle-income countries”. I suggest that the term be slightly altered to “low-to-middle income countries”.
Low middle-income countries has been changed to now read low AND middle income countries

Reviewer 2:
Thank you for directing us to the COS-STAD and COS-STAP guidance. Please see supplementary material 1 and 2 – COS-STAD and COS-STAP standards.
1) The authors say ‘rank’ when the Methods later suggest ‘score’
Now reads score instead of rank:
- of participants to score each generated outcome

2) There is reference to both a two-stage e-Delphi survey and a 3-step Delphi survey - please clarify.
Clarified to read 3 stage delphi process:
- A three-stage international Delphi process

3) COS-STAP standard 2a - ‘Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation’ – more justification about the need for this study should be given. In particular:
(a) Please review other published and ongoing studies (reviews and COS) in the area, e.g. from the COMET database:
http://www.comet-initiative.org/studies/details/740?result=true
http://www.comet-initiative.org/studies/details/1131?result=true
http://www.comet-initiative.org/studies/details/1317?result=true
http://www.comet-initiative.org/studies/details/104?result=true
http://www.comet-initiative.org/studies/details/408?result=true
http://www.comet-initiative.org/studies/details/375?result=true
a) A number of sepsis COS in sepsis have been developed (http://www.comet-initiative.org/studies/details/1317?result=true), including one ongoing in Paediatric Critical Care Medicine research (http://www.comet-initiative.org/studies/details/1131?result=true). No core outcome set currently exists for paediatric sepsis however, and very few are region specific.

(b) What is the rationale for just including stakeholders from LMICs? Why not aim for a globally relevant COS, that includes LMICs? The ‘what should be measured’ may well be the same, even if the ‘how’ may differ by income status.
b) LMIC Stakeholders:
Most research in this area is undertaken in HIC. Outcomes in HIC cannot be reliably extrapolated for use in LMIC. We felt it important if we were creating region specific COS that those working in this setting take ownership to ensure direct relevance to their daily practice.
Now reads:
A minimum of 50 participants for the Delphi panel will be involved. Participants will be recruited from around the world, with an aim to have all from low and middle-income countries. This will ensure a direct relevance to the population of children in most need and give a voice to those rarely heard, a need previously identified in COS development (24)

METHODS
4) Please give the specific link to your study in the COMET database –

Specific link to study added:
Our COS development plan has been registered with the COMET initiative (http://www.comet-initiative.org/studies/details/1400?result=true)

5a) Please add that this is a COS for clinical trials
Specified clinical trials: This COS will be purely focused on clinical outcomes in paediatric sepsis clinical trials in LMIC

b) COS-STAD standard 4, and COS-STAP 3b, requires the scope to include a statement about which interventions the COS will be applicable to, any or particular types; please add this information. This should then be clearly stated in relation to the eligibility criteria for studies in the systematic review.
All forms of published studies will be included. Subjects will children under the age of 18 with sepsis. Those involving a high proportion (>50%) of premature patients will be excluded. Studies undertaken in a low and middle-income country, as defined by the World Bank (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups), and those describing a clinical outcome that is measured systematically across the population studied will be included. All interventions related to paediatric sepsis in this setting will be applicable.

6) Systematic review – do the authors intend to register a fuller protocol for this component with PROSPERO?
Due to the short timeline and the fact we had completed a large part of data extraction prior to October 2019, we did not register the SR with prospero.

7) A reference should be provided for the list of low-middle income countries as defined by the World Bank.
Reference to World Bank added:
(https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)

8) Reviewing published studies will inevitably mean results are for outcomes chosen by trialists several years ago at the time the studies were being designed. Have the authors considered also including ongoing studies in trials registries?
Ongoing trials from LMIC were reviewed on the World Health Organisation International Clinical Trials Platform (ICTRP).

9) COS-STAD standard 8 requires that the initial list of outcomes to be considered should include patients' views as well as those of health professionals. The systematic review of trials is unlikely to cover the former. How will the authors meet this standard?
Given the timeline, we will include the patient-generated ones in round 2 of the delphi. Now reads:
At this point, patients and their parents or guardian will be identified by clinicians known to team members and approached after discharge. The questionnaire will be paper-based and outcome measures simplified into broad domains for the patients to score with the use of a local facilitator. The patient generated outcomes will be incorporated into round 2 of the Delphi.

10. (a) It is usual for there to be some form of validation by a second reviewer, even if only for a sample of studies.
(b) How will the outcome categories be chosen?
(c) How will the results from the systematic review be analysed?
One review author (GW) will perform data extraction using a standardised form. A second reviewer (SM) will provide validation in cases of doubt. The following data will be retrieved: author details, year and journal of publication, sepsis definition, reported outcomes and outcome definition(s). The data

will be synthesised and presented in a descriptive table. The outcomes will then be condensed into a list and placed into broader outcome categories, including efficacy, safety, mortality, morbidity, cost effectiveness and quality of life. Each of these categories will be further stratified depending upon the frequency of outcomes.
A list of authors will be compiled and invited to participate.

11) Stakeholders – COS-STAP 4 '…how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study' - more detail is needed about the process for recruiting participants in the Delphi survey.
Now reads:
Experienced clinicians in paediatrics and critical care, nurses, researchers and previous patients and parents/ guardians will be invited to participate. These will be identified from prior research papers on paediatric sepsis in LMIC, current involvement in ongoing studies and previous collaborations with members of the research team.

12 and 14) Consensus definition
The involvement of patients and their parents or guardians in the Delphi is not clear. The text suggests they will be included through a survey, rather than the Delphi, using a researcher-administered questionnaire. How will ambiguity of language in the questionnaire be avoided (COS-STAD 11)? More detail is required as to how their views will be included in the consensus process, and why they are not participants in the Delphi alongside health professionals and researchers. How many patients and parents or guardians will be included?
Consensus definition - Will the results from all participants be pooled before the definition is applied? See comment 12 above. If so, how will the voices of all stakeholder groups be represented fairly? This comment applies to both the Delphi survey and the consensus meeting
At this point, approximately ten patients and their parents or guardian will be identified by clinicians known to team members and approached after discharge. The questionnaire will be paper-based, and outcome measures simplified into broad domains for the patients to score with the use of a local facilitator, due to the limited access to internet, possible illiteracy and non-English speaking. The patient survey will generate the relevant domains of key interest and be incorporated into round 2 of the Delphi. The specific granular outcomes will be defined by the formal delphi.

13. COS-STAD 9, COS-STAP 8 and 9 – more detail about the analysis of the data is required, including what is meant by 'descriptive statistics
Descriptive statistics will be used to analyse the responses from both round one and two, including quantitative (absolute values, percentages) and qualitative (suggestions given by participants) measures.

15) (a) It is not clear whether all stakeholder groups will be represented at the meeting. For example, will parents or guardians be invited?
(b) The final sentence suggests there will be some consideration of the 'how' to measure the core outcomes. More details about this stage of development, or the plans for this stage, should be given. The authors may wish to refer to the COSMIN-COMET guidance for this - https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1555-2 .
a) Now reads: All stakeholder groups will be represented, including local patients, parents, nurses and clinicians.
b) The next step will be to determine how best to measure the core outcomes using the COSMIN-Comet (26) guidance. Those attending the consensus meeting and prior Delphi participants will be invited to form a group to develop this further

VERSION 2 – REVIEW

REVIEWER	Kirsten Møller Department of Neuroanaesthesiology, Rigshospitalet, University of Copenhagen, Denmark
REVIEW RETURNED	27-Feb-2020

GENERAL COMMENTS	The manuscript has been revised, and I have only one more suggestion for the authors: In the Discussion, you write, “At present, no core outcome sets exist for clinical trials in paediatric sepsis. Outcomes from HICs cannot be reliably extrapolated to LMICs (28).” I suggest rephrasing to, e.g., “At present, no core outcome sets exist for clinical trials in paediatric sepsis in LMICs. Outcomes from HICs cannot be reliably extrapolated to this setting (28).”

REVIEWER	Paula Williamson University of Liverpool, UK I have suggested the authors consider approaches described in papers I have co-authored.
REVIEW RETURNED	12-Feb-2020

GENERAL COMMENTS	(1) The supplementary table 1 related to COS-STAD should state how each standard was or was not met, rather than referencing pages in the text, particularly since not all standards are met. (2) For outcome categorisation, the authors may wish to consider the following taxonomy which is increasingly being used: https://www.jclinepi.com/article/S0895-4356(17)30589-9/fulltext (3) It is not clear how the results of the patient survey are to be ‘incorporated into round 2 of the Delphi’, please give more detail. If the scores given by patients and parents/guardians to the list of outcomes are not to be displayed for Delphi participants to consider in round 2 then this is a limitation which should be discussed. (4) Are the views of the different stakeholder groups (patients/parents/guardians, nurses, clinicians, researchers) expected to be the same? If not, the pooling of results across all groups could mask important differences. Please discuss this issue.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

1) The supplementary table 1 related to COS-STAD should state how each standard was or was not met, rather than referencing pages in the text, particularly since not all standards are met.

• COS-STAD table has been adjusted accordingly. We feel we now meet all the required standards.

(2) For outcome categorisation, the authors may wish to consider the following taxonomy which is increasingly being used:
https://www.jclinepi.com/article/S0895-4356(17)30589-9/fulltext
Now reads:
o The outcomes will then be condensed into a list and placed into one of the 38 domains in the outcome taxonomy (26).

(3) It is not clear how the results of the patient survey are to be ‘incorporated into round 2 of the Delphi’, please give more detail. If the scores given by patients and parents/guardians to the list of

outcomes are not to be displayed for Delphi participants to consider in round 2 then this is a limitation which should be discussed.
Now reads:
o The patient survey will generate the relevant domains of key interest and be incorporated into the outcomes for round 2 of the Delphi. The patient and parent/guardian generated outcomes and associated scores will be displayed to the remaining stakeholders in round two. The specific granular outcomes will be defined by the formal Delphi
o With this knowledge, including the patient scored outcomes, each outcome will be rescored as described previously in Delphi round one

(4) Are the views of the different stakeholder groups (patients/parents/guardians, nurses, clinicians, researchers) expected to be the same? If not, the pooling of results across all groups could mask important differences. Please discuss this issue.
Now reads:
o All outcomes from round two of the e-Delphi survey will be presented, including the results of the patient survey. Both the aggregate score for each outcome and the individual score for each stakeholder group will be displayed in order to ensure any important differences are highlighted and discussed.

Reviewer 1
In the Discussion, you write, “At present, no core outcome sets exist for clinical trials in paediatric sepsis. Outcomes from HICs cannot be reliably extrapolated to LMICs (28).” I suggest rephrasing to, e.g., “At present, no core outcome sets exist for clinical trials in paediatric sepsis in LMICs. Outcomes from HICs cannot be reliably extrapolated to this setting (28).”
Now reads
o At present, no core outcome sets exist for clinical trials in paediatric sepsis in LMIC. Outcomes from HIC cannot be reliably extrapolated to this setting (28).

VERSION 3 – REVIEW

REVIEWER	Kirsten Møller Department of Neuroanaesthesiology, The Neuroscience Centre, Rigshospitalet, University of Copenhagen
REVIEW RETURNED	17-Mar-2020

GENERAL COMMENTS	The paper has been revised, and I have no more suggestions for the authors. Thank you.

REVIEWER	Paula Williamson University of Liverpool, UK I have recommended consideration by the authors of some publications I have co-authored.
REVIEW RETURNED	02-Mar-2020

GENERAL COMMENTS	All requested revisions are satisfactorily addressed. I look forward to reading about the results of this important research.