PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Creation of An Enhanced Recovery After Surgery (ERAS®) Guideline for Neonatal Abdominal Surgery Patients: A Knowledge Synthesis and Consensus Generation Approach
AUTHORS	Gibb, Ashleigh; Crosby, Megan; McDiarmid, Caraline; Urban, Denisa; Lam, Jennifer; Wales, Paul W.; Brockel, Megan; Raval, Mehul; Offringa, Martin; Skarsgard, Erik; Wester, Tomas; Wong, Kenneth; de Beer, David; Nelson, Gregg; Brindle, Mary E

VERSION 1 – REVIEW

REVIEWER	Kevin Elias Brigham and Women's Hospital, USA
REVIEW RETURNED	17-May-2018

GENERAL COMMENTS	The authors present an excellent proposal for ERAS guidelines for neonatal surgery. This is an under-resourced area and one where standards for perioperative care could have a significant impact. The methodologies for determining the patient population and inclusion of elements in the ERAS guidelines were clear. As a proposal, results will likely come in a subsequent publication. The one edit I would suggest is that the authors provide the complete results of the Delphi process. The reader would be interested to known which elements were designated for inclusion as well as which elements the authors felt could be omitted from the protocol.

REVIEWER	Maria Francelina Lopes Centro Hospitalar e Universitário de Coimbra - Hospital Pediátrico, Coimbra, Portugal
REVIEW RETURNED	04-Jun-2018

GENERAL COMMENTS	A well -designed protocol. The application of this protocol to the care of newborns with abdominal surgery will lead to improved health outcomes.

REVIEWER	Arvid Steinar Haugen Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway
REVIEW RETURNED	01-Jul-2018

GENERAL COMMENTS	Review of Manuscript ID: bmjopen-2018-023651; entitled: Protocol for Creation of An Enhanced Recovery After Surgery (ERAS®) Guideline for Neonatal Abdominal Surgery Patients: A Knowledge Synthesis and Consensus Generation Approach. Review

	This manuscript present a development of a protocol for new Enhanced Recovery After Surgery (ERASR) guidelines with aim to integrate evidence-based practices into multimodal care pathways designed to optimize patient recovery in neonatal abdominal surgery. The objective of this study is to improve to create an ERASR guideline to reduce adverse events, enhance quality of care, increase parent satisfaction and reduce health-related expenses. The authors have presented a very interesting protocol for improvement in a vulnerable patient group, neonatal in need of abdominal surgery. The study involves knowledge synthesis, quality assessment and expert consensus to generate an international ERASR guideline. However, there a few issues that need be addressed. The structure of the protocol would benefit from following the IMRAD structure, where objective and aim is at the end of the Introduction section. The authors have provided a para on the Objectives in page 3, lines 33-35. Further, a new para on the aims of the study is listed page 3, lines 48-51. The aims and Objectives are somewhat overlapping, though aims does not include the health related expenses. The authors also mix method and background in the Introduction section, as they in page 4, lines 18-24 describe the outcomes of the ERAS guideline. The outcome should probably be identified through the process of consensus and literature reviews? Hence, placing the outcome as presented here is a bit confusing for the reader. Please amend this para or move it to the Method section. In the Method section, the authors detail the process leading to the scope determination. Several of the topics which reached consensus are already included in the WHO Surgical Safety Checklist (SSC). Use of the WHO checklist is mandatory in most hospitals internationally, also for surgery on pediatric patients, and with no exempts for neonatals. Use of a pediatric version of WHO SSC could influence on patient outcome (addresses several of the listed topics and more). It might not be a part of the ERAS protocols per se, but certainly it is has been proven to influence on patient outcomes in several studies. A recent published stepped wedge cluster RCT (including pediatric patients) have reported effect of WHO SSC on work processes associated to prevention of intraoperative hypothermia and on better timing of antibiotics – and on patient outcomes. The WHO SSC being a mandatory tool to use in surgery in most countries, it is arguable to include use of the checklist in the ERAS protocols as a part of the standardization. Otherwise it would be difficult to assess the true effect of any interventions – could as well be the checklist as ERAS guidelines, if both are being used. The authors need to address this topic in the protocol. For accuracy and consistency, the literature review needs to follow a guideline for protocols like the Equator network's Prisma guideline for systematic reviews. This must to be provided.

	Dates of the evidence consensus has been provided but not for the literature review. Please amend this. Regarding consensus of evidence, it is unclear how the evaluation of the items will be addressed. How will the ratings be scored? Is it a content validity index or will a Kappa analysis be used since it takes uncertainty of the scores into account. How many raters will there be? This information is necessary to provide in the protocol. Independent from the Guideline in itself, there is a need to describe which surveys that are going to be used, preferably validated instruments. Also a description of data collection, data handling, data analysis, type of outcome for the survey etc., should be included. Further, interviews need to be described in more details - sample - recruitment methods - data analysis methodology, development of an interview guide etc. The authors have not presented a sample size calculation for the study of expected improvements of the ERAS guideline on patient outcomes. It is unclear if this protocol includes a study on improvements following implementation of the guidelines, here in a single center for three months and very few patients, with high risk of type II errors, or is merely a development of the ERAS guidelines. If this is misread by me, it probably needs to be better explained throughout the abstract and the MS. If there is going to be a clinical study on the patient outcomes, approval by an ethical board is required prior to study start. Is this protocol valid also for the future implementation study? I would think that such a study would require a separate protocol. This needs to be clarified.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers

Thank you all for reviewing our guideline protocol. We greatly appreciate the efforts and perspectives of reviewers.

We believe we have addressed the questions and concerns. We have also updated the manuscript to reflect our progress along our course of guideline generation during the time of review and provide additional details.

Reviewer: 1
Reviewer Name: Kevin Elias
Institution and Country: Brigham and Women's Hospital, USA

The authors present an excellent proposal for ERAS guidelines for neonatal surgery. This is an under-resourced area and one where standards for perioperative care could have a significant impact. The methodologies for determining the patient population and inclusion of elements in the ERAS guidelines were clear. As a proposal, results will likely come in a subsequent publication. The one edit I would suggest is that the authors provide the complete results of

the Delphi process. The reader would be interested to known which elements were designated for inclusion as well as which elements the authors felt could be omitted from the protocol.

Thank you for your review, your comments and your helpful suggestion.

We have updated our Delphi process-section in our revised manuscript to include our description of agreement/disagreement for the general elements for inclusion. We have now included a list of both the topics voted to be included and those voted to be excluded (Scope Determination, final paragraph). Based on your recommendations and those from reviewer 3, we have also included a measure of interclass correlation to provide an illustration of our raters' overall agreement (Scope Determination, final paragraph).

Reviewer: 2
Reviewer Name: Maria Francelina Lopes
Institution and Country: Centro Hospitalar e Universitário de Coimbra - Hospital Pediátrico, Coimbra, Portugal

A well -designed protocol.
The application of this protocol to the care of newborns with abdominal surgery will lead to improved health outcomes.

Thank you. We anticipate that the eventual guideline resulting from this protocol should have significant impact.

Reviewer: 3
Reviewer Name: Arvid Steinar Haugen
Institution and Country: Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway

This manuscript present a development of a protocol for new Enhanced Recovery After Surgery (ERASR) guidelines with aim to integrate evidence-based practices into multimodal care pathways designed to optimize patient recovery in neonatal abdominal surgery. The objective of this study is to improve to create an ERASR guideline to reduce adverse events, enhance quality of care, increase parent satisfaction and reduce health-related expenses.

The authors have presented a very interesting protocol for improvement in a vulnerable patient group, neonatal in need of abdominal surgery. The study involves knowledge synthesis, quality assessment and expert consensus to generate an international ERASR guideline. However, there a few issues that need be addressed.

The structure of the protocol would benefit from following the IMRAD structure, where objective and aim is at the end of the Introduction section. The authors have provided a para on the Objectives in page 3, lines 33-35. Further, a new para on the aims of the study is listed page 3, lines 48-51. The aims and Objectives are somewhat overlapping, though aims does not include the health related expenses.

Thank you, we have streamlined the wording throughout Introduction to allign the variable goals of this protocol and placed the description of objectives, as suggested, at the end of Introduction.

The authors also mix method and background in the Introduction section, as they in page 4, lines 18-24 describe the outcomes of the ERAS guideline. The outcome should probably be identified through the process of consensus and literature reviews? Hence, placing the outcome as presented here is a bit confusing for the reader. Please amend this para or move it to the Method section.

Thank you. We completely agree. We explored possible outcomes when conceptualizing the study but we are allowing for the process of consensus to identify potential measurable outcomes. We have eliminated this paragraph.

In the Method section, the authors detail the process leading to the scope determination.

Several of the topics which reached consensus are already included in the WHO Surgical Safety Checklist (SSC). Use of the WHO checklist is mandatory in most hospitals internationally, also for surgery on pediatric patients, and with no exempts for neonatals. Use of a pediatric version of WHO SSC could influence on patient outcome (addresses several of the listed topics and more). It might not be a part of the ERAS protocols per se, but certainly it is has been proven to influence on patient outcomes in several studies. A recent published stepped wedge cluster RCT (including pediatric patients) have reported effect of WHO SSC on work processes associated to prevention of intraoperative hypothermia and on better timing of antibiotics – and on patient outcomes. The WHO SSC being a mandatory tool to use in surgery in most countries, it is arguable to include use of the checklist in the ERAS protocols as a part of the standardization. Otherwise it would be difficult to assess the true effect of any interventions – could as well be the checklist as ERAS guidelines, if both are being used. The authors need to address this topic in the protocol.

We enthusiastically agree that there is strong evidence that a well-implemented surgical safety checklist has tremendous potential for improving patient outcomes. We have added sentences concerning the role of the Surgical Safety Checklist (SSC) within a multi-modal ERAS guideline into our discussion of *guideline implementation* and have incorporated the SSC into our *implementation strategy*. Although ERAS guidelines have not traditionally incorporated the SSC, the outcomes of pediatric patients appear to be improved when the SSC is integrated within strong multi-modal implementation strategies. We have therefore emphasized the integration of the SSC into our implementation strategy in a manner that will avoid duplications, assist in checklist tailoring and strengthen the implementation around both the SSC and the ERAS guideline through a common protocol. Our future work to develop and evaluate ERAS implementation success will include evaluation of compliance with the SSC.

For accuracy and consistency, the literature review needs to follow a guideline for protocols like the Equator network's Prisma guideline for systematic reviews. This must to be provided.

Thank you for this comment and the opportunity to expand on the methods used in the knowledge synthesis component of our guideline generation process. We agree that it is very important to demonstrate a systematic approach. We have now included the PRISMA-P checklist (from the

PRISMA-P Statement), and have been careful to outline our process such that it is reproducible, systematic and clear.

The evidence informing previous ERAS guidelines relies heavily on expert knowledge and expert identification of relevant literature. Systematic reviews have not formed a part of previous ERAS guidelines due to the guidelines broad, multimodal qualities. One of the reasons we have pursued publication of this ERAS protocol is to develop, use and publish more rigorous methods and to encourage a more systematic approach to future ERAS guideline development.

The evidence base for the current guideline in development is generated using a series of search strategies that, for feasibility reasons, are modified versions of those of full systematic reviews as described in PRISMA guidelines. Our approach starts with multiple focused search strategies developed with a research librarian similar to that of rapid systematic reviews to provide feasible numbers of abstracts for review for the multiple topics suggested. Using citation searching, focused additional searches and expert identification of relevant publications, as well as searches of the grey literature for guidelines and surveys, we have generated an evidence library for all the topics included. This strategy was deemed most appropriate for a broad-reaching, multi-modal ERAS guideline. To provide illustrations of how we have used this systematic approach across topics, we include examples from different topic areas in the updated manuscript. We provide a sample search strategy for one topic in our proposal (Table 1), added a PRISMA flow diagram of the screening results for a second topic (Figure 1), and a summary table of evidence from a third topic (Supplementary Table 1)

We have rewritten Methods to describe this approach, including our rationale, and provide the PRISMA-P checklist as an illustration of our approach.

Dates of the evidence consensus has been provided but not for the literature review. Please amend this.

We provide this information at the end of our Study Selection Section. As there are still follow-up searches to be performed, our complete dates will accompany the final guideline. This is what we have written in our updated manuscript:

“Initial systematic searches of MEDLINE and CINAHL were performed on December 17th, 2017. Subsequent targeted searches of the peer-reviewed literature were performed within each topic based on the development of subtopics. Additional searches of the grey literature were also performed. The dates of these subsequent searches will be documented in the appendices accompanying the search strategies for all recommendation when the ERAS® guideline is published.”

Regarding consensus of evidence, it is unclear how the evaluation of the items will be addressed. How will the ratings be scored? Is it a content validity index or will a Kappa analysis be used since it takes uncertainty of the scores into account. How many raters will there be? This information is necessary to provide in the protocol.

Thank you. We agree that item evaluation and consensus are very important parts of a guideline

development protocol. Our Methods now provide an expanded description of evidence evaluation and consensus generation. We also agree that it is helpful to have a measure of agreement provided and will include measures of interclass correlation. We have now included the interclass correlation to indicate the rater agreement for the initial scope, population and topic under “Scope determination” as these ratings have been completed at the time of this submission. We have included the number of raters in our manuscript: 10 for the rating of scope, population and topics, and 17 for the recommendations. To provide even greater detail, we will include rating summaries for each recommendation and field notes as supplementary data in our final guideline reports so that readers can appreciate the areas where there is variation in opinion.

Evaluation of the level of evidence supporting recommendations will be performed according to the 2011 Oxford levels of evidence (reference provided in manuscript) by individual teams. This process is now described under “Individual study quality assessment and data synthesis” within Methods. Aggregate quality of evidence and strength of recommendations will be determined by the ERAS working group within a panel following the GRADE recommendations (tables and references provided in manuscript).

There are multiple points at which consensus is obtained: 1. Determination of Scope and population for the guideline; 2. Determination of topics to be addressed; 3. Determination of recommendations for clinical practice; and 4. Determining the aggregate quality of the evidence and strength of recommendations.

Scope, population, and topics were all evaluated and rated by ten members and is described in “Scope determination”. We have described the rating Initial scope and population were rated for necessity for inclusion on a 9-point scale as were topics. Topics were additionally rated for clarity of wording. Recommendations created by working groups will be evaluated by individual ERAS panel members and then discussed as a full panel prior to reworking and re-rating. This process is described under “Consensus of evidence”

Independent from the Guideline in itself, there is a need to describe which surveys that are going to be used, preferably validated instruments. Also a description of data collection, data handling, data analysis, type of outcome for the survey etc., should be included. Further, interviews need to be described in more details - sample - recruitment methods - data analysis methodology, development of an interview guide etc.

The authors have not presented a sample size calculation for the study of expected improvements of the ERAS guideline on patient outcomes. It is unclear if this protocol includes a study on improvements following implementation of the guidelines, here in a single center for three months and very few patients, with high risk of type II errors, or is merely a development of the ERAS guidelines.

If this is misread by me, it probably needs to be better explained throughout the abstract and the MS. If there is going to be a clinical study on the patient outcomes, approval by an ethical board is required prior to study start. Is this protocol valid also for the future implementation study? I would think that such a study would require a separate protocol. This needs to be

clarified.

We thank the reviewer for these thoughtful comments regarding measuring the impact of this guideline and the focus of this protocol. We have tried to answer the questions and concerns and have updated both our manuscript accordingly.

Our protocol is for the development of the guideline itself rather than the evaluation of its effectiveness (either in patient/family outcomes or its feasibility/ acceptability). We recognize that further studies will be an important aspect of evaluating the impact of our guidelines and these will, indeed require development of a separate protocol (or multiple protocols). We have clarified this by retitling the "Guideline implementation" section as "Future Work: Guideline implementation". We have expanded our discussion of the future work anticipated to be undertaken within this section. We have also ensured that our abstract indicates that the purpose of the study is the creation of the protocol and that implementation is a separate study.

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version: 1. Kindly indicate the email address of the corresponding author on your main document which should match the email address information provided in the submission screen.

We have done this.

VERSION 2 – REVIEW

REVIEWER	Arvid Steinar Haugen Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway
REVIEW RETURNED	30-Aug-2018

GENERAL COMMENTS	Review of MS: BMJOP-2018-023651.R1, Protocol for Creation of An Enhanced Recovery After Surgery (ERAS®) Guideline for Neonatal Abdominal Surgery Patients: A Knowledge Synthesis and Consensus Generation Approach. I would like to thank and commend the authors for a thorough revision of the manuscript. They have addressed all the points that were raised. The guideline protocol is well presented and the work performed by the authors is very important for this vulnerable patient group.

VERSION 2 – AUTHOR RESPONSE

Thank you Editors and Reviewers,

We have made the changes suggested and hope that this will be satisfactory.

We have edited our strengths and weaknesses. We now have five total strengths and weaknesses. We have edited these to make clear their relationship to the methods and to keep all points to the length of a single sentence.

We have included the ethics number for the small part of our protocol that will require ethics to complete. We needed to make some minor changes to our protocol after our most recent multidisciplinary meeting. We have submitted ethics and do not anticipate significant delay but are awaiting final approval.