Author’s response to reviews

Title: Relationship between volume and outcome for gastroschisis: a systematic review protocol

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Author’s response to reviews:

Dear Editors,

Thank you very much for your helpful comments regarding our manuscript “Relationship between volume and outcome for gastroschisis: a systematic review protocol” and for giving us the opportunity to revise our manuscript. In the following, we will respond to all the comments. In addition, we uploaded both a ‘clean’ and a ‘marked’ version of our revision; the marked version indicates the changes made to our manuscript during revision via the use of a ‘track changes’ function.

Reviewer #1:
Overall, this is an interesting and well-written manuscript of a study protocol for a systematic review on the relationship between volume and outcome for gastroschisis. Although the planned methods are credible - and remarkably similar to those reported in a previously published study protocol examining (surgical) volume and congenital diaphragmatic hernia [ref. 42] - I think that some reporting aspects could be improved. I have the following minor comments which may be useful for the authors, and potential readers.

- Thank you very much for your review and your positive feedback. We highly appreciate your clear, specific and reasonable comments.
General comment
To clarify, PRISMA/PRISMA-P/SWiM are reporting guidelines, not guidelines for "designing", "developing" or "conducting" reviews. Please, revise the abstract and main text.
- Thank you very much for your general comment on reporting guidelines and for providing us with the interesting article. We revised the corresponding sections as suggested.

Specific comments

Abstract
Page 3. Methods. Lines 60-61. Please, delete "This systematic review protocol has been designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol".
- We deleted the sentence according to your suggestion.
Page 3. Methods. Line 62. Please, include planned coverage limits (e.g. "from inception onwards"). For example: "(…) a systematic literature search (from inception onwards) in MEDLINE, EMBASE, CENTRAL, (…)".
- We included the planned coverage limit according to your suggestion.
Page 3. Methods. Lines 64-66. Please, delete: "We will screen titles and abstracts of retrieved studies, obtain potentially relevant full texts and assess the eligibility of those full texts against our inclusion criteria.". This information is already reported in line 70 (e.g. "Title and abstract screening, full text screening (…) will be conducted by two reviewers independently").
- We deleted the sentence according to your suggestion.
Page 3. Methods. Line 66. The authors' state: "We will include comparative studies (…)". Could you please be more explicit? For example: "We will include comparative studies (e.g. randomised controlled trials, non-randomised controlled trials, and observational studies) (…)".
- We revised the sentence. It now reads: "We will include (cluster-) randomized controlled trials (RCTs) and prospective or retrospective cohort studies analyzing the relationship between hospital or surgeon volume and clinical outcomes"
Page 3. Methods. Line 67. Could you please list the main outcomes for which data will be sought, including prioritization of primary and secondary outcomes, if appropriate. For example: "The primary outcomes will be survival and mortality. Secondary outcomes will be [please, include some examples]"
- We listed the main outcomes according to your suggestion. The sentences read: "The primary outcomes will be survival and mortality. Secondary outcomes will be different measures of morbidity (e.g. severe gastrointestinal complications, gastrointestinal dysfunctions, and sepsis), quality of life, and length of stay."
Background.
Page 5. Lines 86-90. This paragraph was "recycled" from ref. 43. Please, revise. I think it could be deleted, or included/ revised in p.7 if necessary.
- Based on your suggestion, we shortened and slightly revised the paragraph and moved it to another place in the manuscript. The whole paragraph including the revised and moved sentences now reads:
“Management of gastroschisis is not broadly standardized across institutions leading to variability in care between different centers [30]. However, different initiatives started to develop and introduce standardized protocols and pathways for the management and care of gastroschisis [31-33]. Systematic reviews on various other surgical procedures indicate a positive relationship between hospital as well as surgeon volume and clinical outcomes [3-6]. This relationship seems to be stronger for high-risk, low volume procedures [7-10]. Given the characteristics of gastroschisis (long length of stay; need for hospital-based services; multidisciplinary care teams consisting of obstetricians, neonatologists and pediatric surgeons) and the insights on the positive relationship between hospital volume and outcomes for other indications [8], it is plausible that such a relationship might also exist for gastroschisis.”

Methods
Page 8. Lines 153-158. The authors' state: "The protocol follows (...) [PRISMA-P]". Please, revise as follows: "This protocol is reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [41] (see checklist in Additional file 1). The present protocol has been registered within the Open Science Framework platform (registration numbers: osf.io/ex34m; osf.io/hgpz2OSF.IO). Planned methods will be in line with those reported in our systematic review on the relationship between volume and outcomes for congenital diaphragmatic hernia [42, 43]."
- We revised the sentences as suggested.
Page 8. Line 175. Eligibility criteria (Patients). The authors' state: "(...) the subject of the study is gastroschisis; (...). Could you be more explicit? For example: "Patients: We will include studies involving children and adults with gastroschisis"? Only children?). Could you please include diagnostic codes of gastroschisis (e.g. ICD-10, ICD-11?). Please revise/clarify.
- We revised the section on eligibility criteria. The section on patients now reads:
“Patients: We will include studies involving newborns with gastroschisis. We will not use a specific definition for gastroschisis but report the definition used in the corresponding studies.”
Page 8. Line 176. Eligibility criteria (Study design). The authors' state: "(...) the study has a comparative design, we expect to include mostly observational studies, however, if available we will also include subgroup analyses of experimental study designs (e.g. RCTs); (...). Could please be more explicit on study characteristics/design? For example: "Study design: We will include comparative studies, such as randomised controlled trials, non-randomised trials and observational studies (e.g. cohort studies, interrupted time series)" Please, revise/clarify. Note: information on subgroup analyses should be included in Data synthesis subsection, not in "Eligibility criteria". Thank you.
- We revised the section on eligibility criteria. The section on study design now reads:
“Study design: We will include (cluster-) randomized controlled trials (RCTs) and prospective or retrospective cohort studies.”
Page 8. Line 178. Eligibility criteria (Outcomes). The authors' state: "clinical outcomes (e.g. mortality, morbidity) are studied (see "outcomes and priorization")". Could you please be more explicit?
- We revised the section on eligibility criteria. The section on outcomes now reads:
  “Outcomes: We will include studies if at least one of the outcomes listed in the section "outcomes and priorization" is analyzed.”

Page 9. Line 179. Eligibility criteria (Exposure). The authors' state: "volume is assessed as a categorical variable or a continuous variable". Could you please describe the concept of "volume"? Please refer this should be the "exposure". Thank you.
- We revised the section on eligibility criteria. The section on exposure now reads:
  “Exposure/Control: Volume (i.e. hospital volume or surgeon volume) is the number of cases treated or surgeries conducted by a hospital or by a surgeon in a particular period of time. We will include studies if volume is assessed as a categorical variable or a continuous variable and if at least two different hospitals or surgeons are analyzed.”

Page 9. Line 180. Eligibility criteria (Context?). The authors' state: "the study describes more than one hospital or surgeon". Should this refer as context/setting? Please, clarify.
- We now list this criterion in the section on exposure/control as, to our opinion, it matches best.

Page 11. Line 229. Please, rename as "Risk of bias in individual studies".
- We renamed the section as suggested.

Page 11. Line 230-240. Could you please describe other anticipated methods/tools for assessing risk of bias of individual studies (as per your eligibility criteria such as RoB 2.0 for randomised trials? Any other tool for observational studies?) Please, clarify Page 11. Line 246-247. The authors' state: "The synthesis will follow the reporting guideline for synthesis without meta-analysis (SWiM) [50]." Please, revise as follows: "We will report our planned synthesis according to the Synthesis Without Meta-analysis (SWiM) guideline [ref]."
- We added two sentences on the assessment of risk of bias of (cluster-)RCTs. They read:
  “We will use the Cochrane risk-of-bias tool 2.0 (RoB 2) if any individually RCT will be identified [50]. We will use RoB 2 including special issues in assessing risk of bias in cluster-randomized trials mentioned in the Cochrane Handbook if any cluster-RCTs will be identified [51].”
- Also, we adapted the corresponding sentence in the abstract. It now reads:
  “We will systematically assess risk of bias of included studies using RoB 2 for individually or cluster-randomized trials and ROBINS-I for cohort studies, and extract data on the study design, patient characteristics, case-mix adjustments, statistical methods, hospital and surgeon volume as well as outcomes into standardized tables.”
- We revised the sentence on SWiM as suggested.

Page 12. Lines 266-267. The authors’ state: "The systematic review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [54]." Please, delete/revise as follows: "The proposed systematic review will be reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [54]. Any amendments made to this protocol when conducting the study will be outlined and reported in the final manuscript.”
- We revised the sentences as suggested.
Discussion
Pages 13. Please, include brief discussion of any practical or operational issues involved in performing the study you anticipate and any issues not covered in other sections, if appropriate.
- We added the following sentences:
  “Also based on experience from previous work, we expect it sometimes to be difficult to assess whether volume in the primary studies refers to the number of cases treated or to the number of surgeries performed by a hospital or by a surgeon.”

Pages 13. Please, discuss potential limitations at single study level, and at review level you anticipate.
- We added the following sentences to discuss potential limitations:
  “However, based on previous research, we do not expect to find any relevant (cluster-)RCT so that our systematic review will rely on findings from cohort studies. This might limit the certainty of our conclusions. As we restrict eligible studies to English and German documents, this might introduce language bias.”

Pages 13. Please, discuss dissemination plans (e.g. publication in peer-reviewed journals, conferences, interactions with potential knowledge users). For example: "Results will be disseminated through conference presentations and publication in a peer-reviewed journal."
- We added the following sentence:
  “We plan to disseminate results of our systematic review through publication in a peer-reviewed journal.”

Additional files
Please, revise additional files considering all the above (if necessary). Thank you.
- We revised the column “line numbers” of the PRISMA checklist (Additional file 1). The other additional files are not affected by the revisions.

Yours sincerely,

Johannes Morche