To:

Editor in Chief,

World Journal of Meta-analysis

Dear reviewers,

We are pleased to resubmit our manuscript entitled, "Higher Dose of Simethicone Decreases Colonic Bubbles and Increases Prep Tolerance and Quality of Bowel Prep: Meta-analysis of Randomized Controlled Trials". As requested, we have submitted a point-by-point response below to each reviewer's comments as well as a summary of changes below. We found the comments constructive and helpful in the clarification of our study. Unfortunately we are not able to include modifiable figures as these are the outputs we get from our statistical software. Thank you for your consideration.

Below are the point by point responses to the comments of the World Journal of Meta-analysis reviewers and editorial team. Comments and suggestions of the WJM team are italicized.

Reply to Editor:

1) *Change the reference style to superscript with square brackets.*
   This has been done throughout the manuscript

2) *The Authors should review the highlighted text and reword it per the cross check review report.*
   We have modified all the highlighted text and have now highlighted it green in the manuscript. We are citing all the changes herein as well.

   Study Eligibility (last paragraph)
   For a trial of simethicone compared with placebo to qualify for inclusion in this meta-analysis, it should have met the following criteria: 1) prospective randomized controlled trial, 2) comparison of simethicone with placebo, and 3) either bowel preparation quality, bubbles score, ADR, or a combination of any of these parameters was studied.

   Data Extraction (first paragraph)
   One author (MM) extracted data from studies in tabulated data extraction forms and validated by a second author (MH). Extracted data was compared to the original research papers.

Assessment of Study Quality

Bias was assessed by utilizing the Cochrane Collaboration Risk tool which is available in Review Manager 5. There are six criteria which this tool uses to evaluate four bias sources. To assess selection bias, it evaluates adequate sequence generation and allocation concealment. To assess detection and performance bias, it checks whether blinding is effective with respect to personnel, participant, and outcome assessors. To assess attrition bias, it assesses completeness of outcome data. To assess reporting bias, it assesses if selective reporting is present. It also has a protocol to assess other biases such as early withdrawal or extreme baseline imbalances. If a trial excelled in the aforementioned domains it was categorized to lowest risk of bias. If any disagreements occurred among the extracting authors, they were solved by consensus.

Data Synthesis and Statistical Analysis

The software utilized to conduct this meta-analysis is Review Manager (RevMan) v5.3 (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration). Assessments were made under Mantel-Haenszel fixed-effects method with summary risk ratio and 95% confidence interval. Random-effects model was used to combine estimates. If no significant heterogeneity ($p>0.1$) was noted, fixed-effects model was rendered. Statistical tests were 2-sided and $p<0.05$ was considered significant. Effort was made to report 95% confidence intervals with the pooled data. A funnel plot was utilized to evaluate publication bias (inverse standard error for each study was plotted against natural log of the RR (InRR). Heterogeneity was assessed by I2 statistics, with value of more than 40% reported as substantial heterogeneity.

Results Study Identification and Selection (last sentence)

On manual review of the references of retrieved manuscripts, no other studies meeting inclusion criteria were identified.

Assessment of Study Quality

When assessing domains in risk of bias, we noted that all trials had inadequate bias control (Figure 2). The principle risks of bias noted were allocation concealment and participant blinding.

Data Synthesis (first paragraph)

Given that the between-study variability was substantially high for the pooled RR of inadequate bowel preparation, significant colonic bubbles, abdominal pain and distension, the random effects model was employed Since the I2 of the pooled RR of the ADR, nausea, and vomiting was less than 40%, the fixed effects model was utilized for these analyses.

Data Synthesis (last sentence)
No significant publication bias was noted when inadequate bowel preparation outcome was analyzed via funnel plot (figure 6).

Discussion (first paragraph)
Simethicone is polydimethylsiloxane mixture that is frequently prescribed to reduce abdominal discomfort from excessive gas in the bowel. This anti-foaming agent reduces the surface tension of air bubbles so they merge and are easily passed via belching or flatulence.

Discussion (6th paragraph)

Most of the included studies suggest statistically insignificant trends which, when pooled together, do reach statistical significance. Taking into account the multiple countries included, the patient diversity, and uncomplicated administration of simethicone, we believe these results to be generalizable.

3) *Edit and correct Reference 22 and provide website link*
We have corrected the exact location of reference number 22 to 24 and have also provided a link to the reference. We have added two references as well.

Reply to Reviewer #1:

4) *The Authors should pre-specified objectives and methods, and reported the results in accordance with the PRISMA statement.*

This has been added to the manuscript.

The Authors should provide a full search strategy.

This has been addressed in the manuscript under headings of Study identification and Study eligibility.

5) *Authors should clarify the primary outcome (e.g. parameters of inadequate bowel preparation). Outcome definition is particular problem for meta-analyses that rely exclusively on published trial data. Information taken from published articles about the component trials may be incomplete or lack specificity. Publications may not report outcome of interest, and even when the outcome is reported, important details may be lacking*

This is an important point the reviewers raise. We have added as a sentence in the "outcomes for analysis" to clarify this important point.

6) *The Authors should provide a table with the characteristics of patients included in the meta-analysis*

   We did go back and review the included studies. Some studies had not provided the desired characteristics. We did however update the manuscript with data with regard to sex and age from 4 studies.

7) *The Authors should clarify and better explain the results of sensitivity analysis regarding simethicone dose. Sensitivity analyses play an important role in examining the impact of meta-analysis design decisions on the findings as well as the strength of evidence provided by the meta-analysis. The goal of any sensitivity analysis should not be to search for additional findings, but to support and understand the primary findings of the meta-analysis*

   This is an important point raised by the reviewers. We have attempted to rephrase the explanation and we hope this will be clearer to the audience.

8) *Beside the sensitivity analysis performed, the Authors should conduct a meta-regression analysis to evaluate the impact of moderator variables on the results. (e.g. rate of women or patients with previous colorectal cancer)*

   We feel this is a valid recommendation. However, we cannot conduct this analysis because the included studies do not have specific results of bowel preparation with regards to sex or other variables listed by reviewers.

9) *The Authors should provide (maybe in the supplementary materials) the forest plots regarding the analysis of patient compliance. (e.g. nausea, vomiting)*

   These have been included in an added supplementary section.

10) *The assertion "We feel that simethicone as a colonoscopy adjuvant is currently underutilized by gastroenterologists worldwide" requires further deepening.*

    Most bowel preparations utilized in the US and in Europe do not have supplemental simethicone in them and we feel that adding simethicone would help to improve ADR, as well as improve tolerability of the bowel preparation.

Reply to Reviewer #2:

1) *The publication bias is needed to be tested by Egger Test, not only by funnel plot*

Unfortunately, the software we used for analysis does not provide this analysis and therefore we are unable to carry this out.

Please let us know if you have any questions or further concerns. We look forward to hearing from you and are eager to share our report with your viewership.

Sincerely,

M. Madhoun, MD, M Hayat, MD, and I Ali, MD.