

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Oral Mechanical Bowel Preparation for Colorectal Surgery

Draft review available for public comment from July 20, 2013 to August 15, 2013

Research Review Citation: Dahabreh IJ, Steele DW, Shah N, Trikalinos TA. Oral Mechanical Bowel Preparation for Colorectal Surgery. Comparative Effectiveness Review No. 128. (Prepared by the Brown University Evidence-based Practice Center under Contract No. 290-2012-00012-I.) AHRQ Publication No. 14-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

External Peer Reviewers

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Executive Summary	The fact that no definitive decisions can be made with respect to the use of OMBP in patients undergoing various colorectal operations certainly does limit the clinical utility of this report	Thank you for your comment. The report attempts to reflect uncertainty in the data using appropriate statistical methods. We think that it is valuable to know the extent of uncertainty in the evidence used to guide daily clinical decisions.
Peer Reviewer #1	Executive Summary	The limitation [see above] is secondary to a lack of useful evidence to serve as the basis for clinical utility makes this report an essential tool in directing future research and registry construction.	Thank you. No further response necessary.
Peer Reviewer #1	Executive Summary	The key questions are those that we want answered, and yes, they are stated explicitly.	Thank you. No further response necessary.
Peer Reviewer #1	Introduction	Pg 9 Ln 49-51; The Canadian colorectal society guidelines spoke about omitting OMBP for OPEN right and left colon resection; there are no recommendations that OMBP can be eliminated for laparoscopic resection and the SAGES guidelines on laparoscopic resection for colorectal cancer recommends OMBP for laparoscopic cases	We have clarified current guidance on OMBP regarding open and laparoscopic surgery.
Peer Reviewer #1	Introduction	There is an ongoing project that intends to look at OMBP in laparoscopic surgery, but for the purposes of this report, I would think it important to avoid any implications that current data speak to this issue	We agree and have highlighted this is a target for future (ongoing) research.
Peer Reviewer #1	Methods	The search strategies are well detailed and well designed, and the reasons why publications have been included and excluded are clear.	Thank you. No further response necessary.
Peer Reviewer #1	Methods	Including the references used and omitted in the appendix is quite useful as well, since it permits readers the opportunity to appreciate the body of literature that served as the evidentiary basis for the monograph.	Thank you. No further response necessary.
Peer Reviewer #1	Methods	Yes, the outcome measures criteria are appropriate and clear as well.	Thank you. No further response necessary.
Peer Reviewer #1	Methods	I am not qualified to comment on the statistical methodology.	No response necessary.
Peer Reviewer #1	Results	Pg 16 Ln 54; ...although OMBP never appears to be the most likely best choice. In my review, none of the approaches ever seem likely to be the best choice. This statement seems more opinion than restatement of objective observation.	We have removed this sentence. We agree that at this point the analyses indicate substantial uncertainty regarding the optimal OMBP strategy.

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Peer Reviewer #1	Results	The amount of data presented is just about right, and the detail is sufficient to allow the reader a complete view but not overwhelmingly detailed.	Thank you. No further response necessary.
Peer Reviewer #1	Results	The characteristics of the studies are clearly presented as well.	Thank you. No further response necessary.
Peer Reviewer #1	Results	The figures don't offer much in this scenario because the evidence doesn't lead to clear conclusions and decision-making; therefore, the figures cannot be more influential.	We have removed some of the figures from the Executive Summary and have moved some of the figures from the main text to appendices.
Peer Reviewer #1	Results	I do recommend that leading statements, like the one outlined above, be omitted to avoid the introduction of writer bias.	We have removed the sentence regarding the "best" OMBP strategy. Please also see our response regarding the same issue, above.
Peer Reviewer #1	Conclusion	Yes, the major finding is clearly stated, as well as its implication; that no genuine discernible points of clinical advisement are available presently.	Thank you. No further response necessary.
Peer Reviewer #1	Conclusion	The future research section does point out areas where studies are needed, and reviews studies in progress germane to the topic.	Thank you. No further response necessary.
Peer Reviewer #1	Conclusion	It might be reasonable to spell out a study design explicitly that will deliver the information needed, perhaps not in the article, but in a related document or web place, to direct those capable of providing the necessary evidence toward providing it.	We have provided additional study design recommendations, particularly with respect to sample size requirements for superiority and non-inferiority designs, over plausible baseline event rates.
Peer Reviewer #1	General	The report is well organized and presented, and the main points are clearly made	Thank you. No further response necessary.
Peer Reviewer #1	General	If there were clinically relevant conclusions, the structure would be such that this work supports clinical decision-making.	Thank you. No further response necessary.
Peer Reviewer #1	General	Given the limitations of the underlying literature, and the lack of definitive conclusion reached herein, the clinician will understand from reading this piece that no advisement toward optimal clinical decision-making is available presently regarding the use of OMBP prior to colorectal surgery.	We agree that there is substantial uncertainty regarding the most appropriate OMBP strategy. Please note that EPC reports do not make clinical recommendations but focus on reviewing and synthesizing the available evidence.
Peer Reviewer #1	General	The work, however, has achieved its goal.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Executive Summary	The authors have only referred to the use of oral antibiotics on page ES-2 when they say "Antibiotics, parenteral or oral, are also often administered preoperatively for systemic coverage and for reducing the concentration of anaerobic bacteria in the gut" and only two references are cited.	<p>Please note that a comprehensive review of the role of oral antibiotics in the preparation of patients for colorectal surgery was out of the scope of this review. We have provided details for the included studies regarding the use of oral antibiotics (additional information has been extracted and will be made available online). However, our search strategies and study selection criteria did not allow us to perform any analyses regarding the benefits and harms of oral antibiotics.</p> <p>We realize that the use of oral antibiotics (alone or in combination with OMBP) is an active research area with interesting emerging observational data. For this reason we have addressed issues related to their evaluation in future research studies in the Discussion section of the revised report.</p>
Peer Reviewer #2	Executive Summary	There is a substantial published literature with prospective, randomized, placebo controlled trials that verify the use of oral antibiotics with mechanical preparation compared to mechanical preparation alone.	<p>Please note that a comprehensive review of the role of oral antibiotics in the preparation of patients for colorectal surgery was out of the scope of this review.</p> <p>The studies described by the reviewer (oral AB + OMBP versus OMBP) cannot provide information on the main effect of OMBP (which was the target of our review). Please also see our reply to the preceding comment.</p>
Peer Reviewer #2	Executive Summary	There are meta-analyses which show that oral antibiotics with mechanical preparation and systemic antibiotics yield lower infection rates than mechanical preparation and systemic antibiotics only, but these are not identified anywhere in this manuscript	Please see our reply to the preceding comment.
Peer Reviewer #2	Introduction	The introduction does not give a perspective of the work of Edgar Poth and others of 60-70 years ago who documented that mechanical preparation is not of value.	Thank you for providing these references. We have provided some historical context regarding the evolution of preparation for colorectal surgery over time, however we base our analyses on studies selected using the criteria described in the Methods section of the report.

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Peer Reviewer #2	Introduction	The introduction implies that the practicing community has been totally misdirected about mechanical preparation.	We did not mean to imply any misdirection of the clinical research community, and we have carefully reviewed the text to avoid any misunderstandings. We note that several other reviewers found the Introduction to be informative and balanced.
Peer Reviewer #2	Methods	The methods for identifying the articles are fine, except that it has ignored the entire literature on the oral antibiotic bowel preparation.	Please see our above-listed replies regarding the review scope. As mentioned, a comprehensive review of the role of oral antibiotics in the preparation of patients for colorectal surgery was out of the scope of this review.
Peer Reviewer #2	Results	The results are fine for as far as they have gone	Thank you. No further response necessary.
Peer Reviewer #2	Discussion	The future research direction makes a passing reference to the use of oral antibiotics.	We have expanded this section to provide more concrete recommendations regarding future research.
Peer Reviewer #2	Discussion	The foundation for the future research section is lacking from the discussion delivered earlier in the manuscript.	We have provided additional concrete suggestions for future research activities.
Peer Reviewer #2	Conclusion	We do not need any more randomized trials of mechanical preparation with the same old products. Newer cleansing agents may be useful, and certainly newer antimicrobial strategies need to be pursued.	We have provided recommendations for future research that go beyond randomized trials. However, valid estimates of treatment effects are ideally obtained from randomized trials. We have discussed designs that can be used to evaluate the effect of oral antibiotics in combination with OMBP. We also provide power calculations for establishing superiority and non-inferiority.

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Peer Reviewer #2	Conclusion	The authors have stated “We believe that there is need for a large, pragmatic and definitive RCT examining all combinations of using versus not using OMBP, oral antibiotics, and enema prior to colorectal surgery.” There is already a strong body of evidence that supports the use of 1) mechanical bowel preparation, 2) oral antibiotic preparation, and 3) appropriate systemic antibiotic all used together for the optimum prevention of surgical site infections in elective colon surgery.	<p>First, this report did not examine the main treatment effects of oral or parenteral antibiotics (we only examined them as co-interventions). Thus, we cannot discuss the strength of evidence regarding points #2 and #3 in the reviewer’s comment.</p> <p>Regarding point #1, we found that randomized trials have not produced conclusive results regarding the benefits and harms of OMBP. For all but four outcomes, the credible intervals around summary estimates were very wide, indicating substantial uncertainty regarding the comparative effectiveness of OMBP and no preparation or enema. For the remaining four comparisons of OMBP versus no preparation (all-cause mortality, leakage, wound infection and peritonitis) credible intervals were somewhat tighter (but still included the null value), leading us to conclude that the strength of evidence was low for “lack of difference”.</p>
Peer Reviewer #2	Conclusion	Studies that continue to re-iterate the same conclusions with the same trials of mechanical preparation alone are of no value. It is like studying bicycles without tires: they do not go very fast.	We believe that our analyses are the first to fully illustrate the amount of uncertainty in the existing trials of OMBP. For example, numerous reviews have used (in our opinion) inappropriate statistical models that assume the “true” effect of OMBP to be the same across studies. Our analyses better reflect uncertainty and can provide more reliable guidance for the planning of future research.
Peer Reviewer #2	Conclusion	The oral antibiotics must be a component of the mechanical bowel preparation and that is the scientific basis for cleansing the colon. It puts the tires back on the bicycle.	We appreciate the emphasis placed by the reviewer on oral antibiotics. Please see our replies above regarding the scope of the review (OMBP was the focus, not oral antibiotics) and the steps we have take to address the role of oral antibiotics in future research on OMBP.
Peer Reviewer #2	General	The role of oral antibiotics with the mechanical preparation has been omitted. This is the key question, and not whether mechanical preparation is of any value.	Unfortunately, this was not the Key Question posed by the nominator or one that emerged in extensive discussions with Key Informants and Technical Experts. As we have detailed in our replies to preceding comments, the use of oral antibiotics was not within the scope of the review.

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Peer Reviewer #2	General	The manuscript is organized well. It is just not inclusive of the entire subject; specifically, the role of oral antibiotics with mechanical preparation.	Thank you for your comment. Please see our responses above regarding the inclusion of studies on oral antibiotics.
Peer Reviewer #2	General	This manuscript reviews the published literature on the subject of whether mechanical bowel preparation reduces surgical site infections, including anastomotic leakage	Thank you for reviewing this report. No further response necessary.
Peer Reviewer #2	General	As has been identified in previous Cochrane reviews with attendant meta-analyses and meta-analyses by others, the authors have concluded that evidence supports that mechanical preparation of the colon can be omitted.	We respectfully disagree with this interpretation of our results. We found weak evidence suggesting that OMBP has similar effectiveness with no preparation with respect to all-cause mortality, anastomotic leakage, wound infection, and peritonitis for patients undergoing elective surgery for colorectal cancer. However, the evidence base was too weak to confidently exclude either modest benefit or modest harm. Evidence for other outcomes and comparisons was insufficient to draw definitive conclusions.
Peer Reviewer #2	General	They also site the Canadian Society of Colon and Rectal Surgeons as issuing guidelines that mechanical preparation should be omitted.	Thank you. No further response necessary.
Peer Reviewer #2	General	The European Enhanced Recovery After Surgery (ERAS) Society has recently made similar recommendations	We have refrained from citing ERAS guidelines because they refer to bundles of interventions. Similarly, trials of ERAS were not considered in the report because they cannot be used to identify the effect of OMBP from the other bundled interventions.
Peer Reviewer #2	General	It can certainly be said that mechanical preparation of the colon alone is not of benefit in the reduction of surgical site infection, as was documented by dedicated surgical investigators of the 1930s and 1940. In my perspective, the manuscript is a re-iteration of evidence that has been present in the surgical literature for 70 years. This does not need to be studied any further unless a unique component to the mechanical preparation can have antimicrobial or modulation activity against the potential pathogens of the colon.	We respectfully disagree with this interpretation of our results. We found weak evidence suggesting that OMBP has similar effectiveness with no preparation with respect to all-cause mortality, anastomotic leakage, wound infection, and peritonitis for patients undergoing elective surgery for colorectal cancer. However, the evidence base was too weak to confidently exclude either modest benefit or modest harm. Evidence for other outcomes and comparisons was insufficient to draw definitive conclusions. We have provided concrete suggestions regarding future research that could clarify the relationship between OMBP and oral antibiotic use on effectiveness.

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Peer Reviewer #2	General	The manuscript is obviously well written and is very thorough in addressing the recent barrage of literature that is attacking mechanical preparation alone. For this to be of acceptable quality, it must address the scientific basis of using oral antibiotics with the mechanical bowel preparation. To do otherwise, is to misdirect the practicing community on the road to enlightened prevention of surgical site infection in elective colon surgery.	Thank you. Please see our replies to comments from the same reviewer regarding the interpretation of our results and the need to further investigate the relationship between OMBP and oral antibiotics.
Peer Reviewer #3	Introduction	Clearly written.	Thank you. No further response necessary.
Peer Reviewer #3	Introduction	They state that there were no RCT to support bowel prep, But Nichols and Condon published a multi-center trial in the 70s to support bowel prep with antibiotics. They state secular trends do not support looking at this issue, but in the two large multicenter observational studies (one private sector and one VA), oral antibiotics are still used in 35-40% of patients.	We have reviewed several papers by Drs. Nichols and Condon and we have included any that met our selection criteria. Please note that studies comparing the use of oral antibiotics versus not were not within the scope of the review (unless patients also received alternative OMBP treatments).
Peer Reviewer #3	Methods	There seems to be considerable bias among the authors that the role of oral antibiotics does not need further study.	To the contrary, we have provided specific recommendations for future research on oral antibiotics in association with future research on OMBP.
Peer Reviewer #3	Results	They try to look at harm although many studies were not powered to study harm.	We agree that many of trials were not designed to evaluate harms and for that reason we have also considered NRCS and single group studies. As an aside, whether a study was "powered" to evaluate harms has no bearing on the interpretation of study results once the data have been collected and analyzed.
Peer Reviewer #3	Results	The amount of effort devoted how they looked at key question 2 given the lack of data is distracting.	We have presented the evidence (and the methods used to identify and appraise it) for all predefined outcomes. We do not believe that the presentation is distracting.
Peer Reviewer #3	Discussion	The future research is clear, but again needs to be more transformative:	We have increased the specificity of our recommendations for future research.
Peer Reviewer #3	Discussion	Should we study oral antibiotics without prep?	We have addressed this issue in the revised report (see Discussion, Future Research Needs).
Peer Reviewer #3	Discussion	How does enhanced recovery factor in?	We have addressed this issue in the revised report (see Discussion, Future Research Needs).

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Peer Reviewer #3	Conclusion	I don't think we need any more studies of mechanical prep alone to no prep.	We respectfully disagree with this conclusion. We have expanded on our rationale for recommending a new trial.
Peer Reviewer #3	Conclusion	Yes, the report is clear but the findings are not new or different from Cochrane analyses.	In the Discussion section we have highlighted the differences between our work and the Cochrane review on the same topic.
Peer Reviewer #3	Conclusion	It is unclear how they will inform, or possibly misinform policy decisions.	Hopefully, the up-to-date summary of the evidence that we provide, together with the use of statistical methods that fully account for data uncertainty can inform clinical practice and the design of future research. Please note that EPC Evidence Reports do not make clinical or policy recommendations.
Peer Reviewer #3	General	There are twelve meta-analyses or systematic reviews on this topic including 5 in the Cochrane database since 2000	We have expanded the discussion of differences between our work and previous systematic reviews.
Peer Reviewer #3	General	While the key questions are explicitly stated, they did not have evidence to answer many of them.	We agree that there is insufficient evidence to answer the Key Questions posed by this review. Hopefully our analyses and recommendations for future research can provide some guidance for investigators in this field.
Peer Reviewer #3	General	They totally ignore whether oral antibiotics with or without mechanical bowel preparation are important. Two large observational studies confirm the finding of this analysis - mechanical bowel prep offers no protection from surgical site infection, however, patients receiving oral antibiotics with or without mechanical prep had a 50% reduction in the adjusted odds of surgical site infection. This should really be a key question. The field moved away from oral antibiotics prior to moving away from mechanical prep, such that many recent trials did not include oral antibiotics.	<p>Please note that a comprehensive review of the role of oral antibiotics in the preparation of patients for colorectal surgery was out of the scope of this review. We have provided additional details for the included studies regarding the use of oral antibiotics. However, our search strategies and study selection criteria do not allow us to perform any analyses regarding the benefits and harms of oral antibiotics.</p> <p>We realize that the use of oral antibiotics (alone or in combination with OMBP) is an active research area with interesting emerging observational data. For this reason we have addressed issues related to their evaluation in future research studies in the Discussion section of the revised report.</p>
Peer Reviewer #4	Introduction	The introduction is clear, concise, and easily understood.	Thank you. No further response necessary.

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Peer Reviewer #4	Introduction	The inclusion exclusion criteria are justifiable and the search strategies are explicitly stated and logical.	Thank you. No further response necessary.
Peer Reviewer #4	Methods	The statistical methods used seem quite appropriate as do the definitions for the outcome measures.	Thank you. No further response necessary.
Peer Reviewer #4	Results	The details presented are appropriate and appropriately comprehensive.	Thank you. No further response necessary.
Peer Reviewer #4	Results	The characteristics of the study are well described and all the key messages are explicit and applicable.	Thank you. No further response necessary.
Peer Reviewer #4	Results	The tables, figures, and references are very appropriate.	Thank you. No further response necessary.
Peer Reviewer #4	Results	The only studies which the authors overlook are not randomized controlled trials and could not be used in meta analysis but are very clinically relevant. Specifically the authors should focus upon the value of mechanical bowel preparation when laparoscopic surgery is performed. The value of having a decompressed empty colon as well as the extreme importance of being able to visualize endoscopically irretrievable lesions, transitions from normal to abnormal mucosa, and small cancers is very important. Moreover, the potential to visualize the mucosa both prior to and after an anastomosis cannot be under emphasized. Thus, although the authors focused upon infection and co-morbidity, they have not addressed the value of mechanical bowel preparation to facilitate and enhance the safety of laparoscopic surgery. Some discussion of this topic needs to be included.	We reviewed studies that met predefined inclusion criteria, determined through a careful process of topic development and refinement, and extensive discussions with technical experts. To accommodate the reviewer's suggestion, we have provided some additional discussion of issues related to the evaluation of OMBP in the setting of laparoscopic surgery in the revised report.
Peer Reviewer #4	Discussion	The implications and major findings are clearly stated.	Thank you. No further response necessary.
Peer Reviewer #4	Discussion	The limitations of the review studies are indeed adequately described.	Thank you. No further response necessary.
Peer Reviewer #4	General	This report is very clinically meaningful having appropriately posed and answered almost all of the key questions.	Thank you. No further response necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	The report is well structured and organized.	Thank you. No further response necessary.
Peer Reviewer #5	Introduction	The introduction provided a clear outlining of the background and need for this systematic review.	Thank you. No further response necessary.
Peer Reviewer #5	Introduction	I have no clinical knowledge of the subject matter, but was still able to understand the procedures and different interventions involved in oral mechanical preparation for colorectal surgery.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	Search strategies and study selection seem appropriate and carried out correctly.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	The authors have outlined a well-defined PICOT and seemed to correctly assess risk of bias.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	The authors have correctly done meta-analysis based on clinical and methodological homogeneity prior to computing statistical heterogeneity and have also correctly chosen to analyze randomized and non-randomized studies separately.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	The choice of odds-ratio as the unit of analysis is acceptable. While risk ratios are more comprehensible to the general readers, I think odds ratios are more consistent between studies, and also the unit of choice in the Bayesian network analysis the authors have also undertaken.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	By choosing odds ratios for the standard meta-analyses as well, they ensure a consistent comparison across the two types of analysis.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	The decision to supplement (and perhaps even supersede) the standard meta-analysis with a Bayesian network meta-analysis is very appropriate in this case as the authors are presented with a limited amount of interventions compared amongst each other.	Thank you. No further response necessary.
Peer Reviewer #5	Methods	The methods, software, and choice of priors for this analysis all seem to be appropriate for the situation.	Thank you. No further response necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Methods	I do have a couple of concerns with the following statement on page 11 lines 28-32: "Studies comparing enema alone and no OMBP or enema were not in the scope of this report, and such studies (if any exist) are not included [in] the analyses. This does not induce any bias in estimates of the treatment effects obtained from comparisons reported in the included studies." (note the typo). Firstly the authors state that these studies are outside the scope of the review, yet on page 40, Table 6, the authors list all the indirect results from the network analyses for the comparison of enema vs no preparation. Is this not a contradiction? If they are going to present these results, would it not be informative to have the direct comparison studies to augment this information? Secondly, even if we concede that this comparison is not within the scope of the review, the studies comparing enema to no preparation would still inform the other comparisons indirectly within the network meta-analysis, so I'm not sure the authors statement that the exclusion of these trials does not induce bias can be taken at face value--(I agree it is true for the direct meta-analyses, but not necessarily for the network analyses). I think the authors need to better justify their decision not to include these studies in their review.	<p>Under the assumption that data is missing (completely) at random, we believe our comment about the absence of bias to be correct. Both pairwise and network meta-analyses may be biased if selection processes are operating in a given research field. It is not clear how these processes could be modeled adequately, specifically regarding the use of OMBP in colorectal surgery.</p> <p>The fact that a group of studies was not deemed within the scope of the report (for feasibility reasons) does not imply that indirect estimates are biased or that they should not be reported. In the Final Report we have clarified how these estimates were obtained and have clearly indicated them as indirect. We prefer not to drop these results entirely.</p>
Peer Reviewer #5	Results	The results section is well organized and clearly presents the authors' findings.	Thank you. No further response necessary.
Peer Reviewer #5	Results	In the standard meta-analysis sections, outcomes are listed with forest plots where necessary and interpretations of results seem appropriate and clear.	Thank you. No further response necessary.
Peer Reviewer #5	Results	For the network analyses, pairwise results are presented in table forms, which is appropriate given the small number of interventions.	Thank you. No further response necessary.
Peer Reviewer #5	Results	The rank probability graphs are interesting, but they are a little hard to interpret. One suggestion to improve them would be to include the SUCRA calculation (see Salanti G, ADes AE, Ioannidis JP. 2011 Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 64(2): 163-71) which allows the reader to more easily determine which treatment has the better probability rankings.	Strictly speaking, the area is undefined for discrete distributions (such as ranks). We think that such presentation would be somewhat strange in this particular case, because only 3 values are possible (1-2-3). We have opted not to use SUCRA.
Peer Reviewer #5	Results	The summary figures for the active OMBP strategies take a little bit of time to understand, but I think in the end they are a nice way of summarizing this bunch of clinically heterogeneous data.	Thank you. No further response necessary.

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Peer Reviewer #5	Results	No other issues with the results. Figures and tables are easy to follow and I don't see any gaps in the selection of studies etc.	Thank you. No further response necessary.
Peer Reviewer #5	Discussion	Their use of confidence intervals to interpret both statistical and clinical significance of findings is commendable.	Thank you. No further response necessary.
Peer Reviewer #5	Discussion	Their lists of limitations and evidence gaps are appropriate and this is generally reflected in their cautious interpretations and list of future research needs.	Thank you. No further response necessary.
Peer Reviewer #5	Discussion	Perhaps one issue that needs to be elaborated on is the authors' suggestion of doing an individual patient meta-analysis. In my experience this is rarely possible, and probably impossible if many of the studies are very old (which seems to be the case here according to figure 3). I would like the authors to expand a bit on how they feel this could be done with the current set of studies. Would it be done only on a subset of the most recent studies (and even then only on the ones that cooperate and are willing to surrender their individual patient data)?	We have suggested that the individual patient data meta-analysis could be focused on recently conducted trials of OMBP vs. enema or no preparation.
Peer Reviewer #5	Conclusion	I think the authors were correctly cautious in interpreting and making conclusions based on the results of the analyses.	Thank you. No further response necessary.
Peer Reviewer #5	General	Overall this report is very well conducted, written, and organized in a way that makes it easy to follow and understand what the authors did	Thank you. No further response necessary.
Peer Reviewer #5	General	Key questions were explicitly stated and I believe sufficiently addressed within the scope of the review.	Thank you. No further response necessary.
Peer Reviewer #5	General	I have no issues with the structure, clarity, and usability of the report.	Thank you. No further response necessary.
Peer Reviewer #5	General	Aside from the specific comments made in other sections, I think this was an exceptionally well written review and the authors are to be commended.	Thank you. No further response necessary.
Peer Reviewer #5	General	There were some formatting issues, that may have been just with the version I printed out, but I will mention them. Specifically Figure 11 (page 34) seemed to cut off some of the text and same (but to a lesser extent) for figure 13 on page 40.	Thank you. This typesetting error seems to be caused by an incompatibility between our software and the PDF conversion software used by the online submission system. We have made sure that the problem does not appear in the revised report.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	I did find a couple of minor typos the authors will want to fix:	Thank you. Please see below.
Peer Reviewer #5	General	Page 1, line 43: "...a recent large raandomized trial of found that the rate...."; delete the word "of" or finish the phrase.	Thank you spotting this typo. We have corrected it.
Peer Reviewer #5	General	Page 2, line 22: "(approximately 2 litters)"; should read "liters".	Thank you spotting this typo. We have corrected it.
Peer Reviewer #6	Introduction	Well written and states the objectives clearly.	Thank you. No further response necessary.
Peer Reviewer #6	Methods	The inclusion and exclusion of the articles reviewed was good.	Thank you. No further response necessary.
Peer Reviewer #6	Methods	The analytical process and methods were sound.	Thank you. No further response necessary.
Peer Reviewer #6	Results	The results were inconclusive or did not distinguish a difference between non bowel prep and a bowel prep. The main reason for the inability to identify a difference is the heterogeneity of the studies -- parameters measured and methods. Their analysis attempted to overcome these issues but they arrived at the same conclusions.	Thank you. We believe that this is a fairly accurate summary of our results.
Peer Reviewer #6	Discussion	The future research section lacks specifics.	We have provided more concrete research recommendations.
Peer Reviewer #6	Discussion	After this extensive analysis and understanding of the weaknesses of each study, the authors should be able to provide a detailed study design that would be able to provide a more definitive answer to an issue that has not been answered with 40 RCT, 8 NRCS.	Please note that the 40-or-so RCTs have addressed comparisons across different interventions. Also, among RCTs addressing the comparison of OMBP versus no-OMBP, several have been too small to reach reliable conclusions. We have provided detailed suggestions for the design of future OMBP studies.
Peer Reviewer #6	Conclusion	Their conclusions are clearly stated and justified. It is more that this analysis does not add any significant findings to those already published.	Thank you. We believe that all previous analyses have underestimated the uncertainty in the available data. We believe that our results can help guide clinical practice and the planning of future research studies.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	This is an extensive and thorough analysis.	Thank you. No further response necessary.
Peer Reviewer #6	General	However, it does not add much to the recent Cochrane review as far as recommendations for practice parameters.	In the Discussion section we have provided a summary of the differences between our work and the Cochrane report. We believe that our (more conservative) interpretation of the evidence is more appropriate. We have based our conclusions on analyses that fully account for the uncertainties in the available data (in ways that the Cochrane review does not).
Peer Reviewer #6	General	The report is well organized and written.	Thank you. No further response necessary.
Peer Reviewer #6	General	However, due to the issues raised above and the inconclusive findings, this report cannot be used to support one practice over another. It's unclear if it can honestly say that both practices are equivalent.	We agree with this interpretation of our results and hope that our future research needs recommendation will be useful to researchers in this field.
Peer Reviewer #7	Methods	Methods are well described and are appropriate.	Thank you. No further response necessary.
Peer Reviewer #7	Results	The results are described in great detail.	Thank you. No further response necessary.
Peer Reviewer #7	Results	The summary of results is key for the average reader.	Thank you. No further response necessary.
Peer Reviewer #7	Discussion	Discussion is excellent.	Thank you. No further response necessary.
Peer Reviewer #7	Discussion	Should address the issue of oral antibiotics and compliance with OMBP more completely.	We have provided additional Discussion on oral antibiotics in the Discussion section, particularly with respect to Future Research Needs.
Peer Reviewer #7	Figures	Figures 11 and 13 have the legends obscured by the figure.	Thank you for pointing this typesetting error. We have made sure that it does not affect the revised report.
Peer Reviewer #7	General	Very well done and thorough evaluation of the current literature on OMBP.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	There remain several typographical errors throughout the manuscript that need to be addressed before publication.	Thank you. We have corrected all typos brought to our attention.
Peer Reviewer #7	General	The authors provide limited discussion as to the role of oral antibiotics with OMBP. Was it possible to perform an analysis of OMBP with oral antibiotics compared to other groups?	We have expanded somewhat the future research recommendations with respect to oral antibiotics. We have provided information on the use of oral antibiotics in the primary studies (and complete study-level information will be made available online). Please also see above regarding our ability to perform analyses of the treatment effect of oral antibiotics in the available data.
Peer Reviewer #7	General	A discussion concerning the completion of OMBP. The literature is based on whether OMBP is prescribed. The issue of compliance is important and should be discussed especially when considering future studies.	Unfortunately this was not one of the predefined outcomes for our review. Also, it is not clear if using "completion of OMBP" as an outcome would provide actionable information, because this information (by definition) is unavailable when the decision to use or not use OMBP is made.
Peer Reviewer #7	General	Report is well structured and organized.	Thank you. No further response necessary.
Peer Reviewer #7	General	Main points are clear.	Thank you. No further response necessary.
Peer Reviewer #7	General	The review makes an effective case for RCTs to answer the questions; however, the review may want to provide more guidance as to what an effective RCT would look like since there are many possible comparisons and many co-interventions to consider.	We have provided more concrete recommendations for the design of future studies in the Discussion section of the revised report.
Peer Reviewer #8	Executive Summary	Yes, since surgeons in US clearly has not abandoned OMBP in colon surgery and the evidence for abandoning OMBP in anterior resection of rectum is not is not clearly evidence based.	Thank you. No further response necessary.
Peer Reviewer #8	Executive Summary	Key question 1 is well defined, but in my opinion already answered regarding to colon surgery by two large RCT's, also acknowledged by the Canadians. The explicit need for this is not declared in the Introduction/summary. It seems that the most important reason is that the largest RCT's are European.	We believe that the analyses we present clearly indicate that there exists substantial uncertainty regarding the effectiveness and safety of OMBP. Please see above and also the strength of evidence assessment in the Final report regarding the interpretation of the evidence.
Peer Reviewer #8	Methods	As a Meta analysis the inclusion criteria of the studies are clear, but described in a somewhat confusing way.	Thank you. We have tried to provide a detailed description of the selection criteria. The ES presents a more streamlined version.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Methods	My expertise does not allow me to state whether the statistical methods are appropriate.	Thank you. Please note that a statistical reviewer provided a critique focusing on the statistical methods. Please see above for our replies to his comments.
Peer Reviewer #8	Methods	Is there really a need for these diversified stats for the main question (OMBP or not regarding to 30-day morbidity and mortality)?	We have tried to simplify the Executive Summary to make it more user-friendly. We think that complex data require advanced methods to yield meaningful answers, particularly with respect to the uncertainty of the underlying evidence.
Peer Reviewer #8	Results	Very detailed results section.	Thank you. No further response necessary.
Peer Reviewer #8	Results	For me hard to understand the important message and some of the graphs hard to understand, though I could not find any errors.	Thank you for your comment. We have tried to streamline the ES to make it more user-friendly.
Peer Reviewer #8	Results	In page 14, line 18 there seems to be a numerical mistake (15 RCTs and 5 NRCSs does not equal 20 adult and 1 mixed population).	Thank you for pointing out this error. We have corrected it.
Peer Reviewer #8	Discussion	I agree that possible negative effects should be better studied compared to no OMBP.	Thank you. No further response necessary.
Peer Reviewer #8	Discussion	The authors discuss the difference between older and newer studies, however they state that most of the studies are small, which is true if you only consider the number of studies. There are, however 2 large randomised studies, similar in design, which recruit more than 2500 patients, which is an important issue.	We agree that 2 studies (Contant et al. and Jung et al.) are fairly large. We have clarified that we were referring to the majority of studies when discussing small sample sizes. The power calculations provided in the Discussion section can give some perspective on what is an "adequate" sample size for the event rates and relative risks observed with OMBP.
Peer Reviewer #8	Discussion	This matter is not discussed nor do the authors discuss that these studies tested the need of OMBP in both right- and left sided colon resection.	We have provided additional information regarding the inclusion of right- and left-sided resections.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Conclusion	It though true that omitting OMBP in rectal cancer surgery is not evidence based. The conclusion seems not to be solid in my point of view.	Our interpretation of the available evidence is reflected in our assessment of the strength of evidence. Briefly, we found weak evidence suggesting that OMBP has similar effectiveness with no preparation with respect to all-cause mortality, anastomotic leakage, wound infection, and peritonitis for patients undergoing elective surgery for colorectal cancer. However, the evidence base was too weak to confidently exclude either modest benefit or modest harm. Evidence for other outcomes and comparisons was insufficient to draw definitive conclusions.
Peer Reviewer #8	Figures	some of the graphs hard to understand	We have provided additional information in some figure legends to facilitate interpretation.
Peer Reviewer #8	General	The report is very detailed, maybe too detailed	We have streamlined the Executive Summary to focus on key findings; we have also moved some of the details of the analysis to the Appendix.

Technical Expert Panel Members

Commentator & Affiliation	Section	Comment	Response
TEP #1	Abstract	Pg v: You might want to make clear that by "effectiveness" and "outcomes" you are generally referring to complications that possibly could be avoided by OMBP whereas by "harms" you are referring to adverse events that could be directly attributed to the prep (and not a failure of its efficacy).	We have clarified as suggested.
TEP #1	Abstract	Pg v, lines 41-2: Perhaps include the statement from pg ES-14 that you cannot exclude a modest (30-50%) change in odds in either direction. The emphasis is on modest! It's a helpful piece of info.	We have rephrased the Conclusions paragraph of the abstract to incorporate this idea.
TEP #1	Executive Summary	ES-1 Line 15: Maybe add: "; however, we did not study the efficacy or safety of OMBP for those indications"	Thank you for this suggestion. We have added a clarifying footnote.
TEP #1	Executive Summary	ES-1 Line 45: Maybe add "elective" so the reader has no confusion, i.e. "percent of all elective colorectal surgeries."	We have rephrased as suggested.
TEP #1	Executive Summary	ES-3 Line 48: I vaguely remember discussing venous thromboembolism in our conference call but I can't remember thinking it was an important outcome. Are there data indicating that OMBP might or might not be a risk factor for VTE?	The issue of VTE was discussed (in varying levels of details) in each of the TEP teleconferences we held. We decided to include VTE (DVT and PE) outcomes in our review, however the available evidence was limited. Although a specific pathogenetic mechanism has not been established, some experts suggested that use of OMBP may prolong hospitalization or slow the rate of recovery post-surgery, and in that way increase the risk of VTE (due to limited mobility).
TEP #1	Executive Summary	ES-5 Line 51: Might it be worth giving some idea of the size and potential influence of the retracted paper and whether it was included in the recent Cochrane review? Just a thought.	The appendices include detailed sensitivity analyses after including the retracted study. We have tried to limit the emphasis on this study in the main text, given the uncertainty regarding the veracity of the information reported in it.
TEP #1	Executive Summary	ES-5 Line 54: Maybe add "each" so "(each with or without enema)"	We have rephrased as suggested.
TEP #1	Executive Summary	ES-6 Line 9: I'm a bit surprised that 20 of 46 OMBP trials omitted peri-op antibiotics. I thought these were considered a well-validated intervention for bowel surgery even in Europe. Can you make any estimate of the effect of the antibiotics in those 46 OMBP trials? (You probably commented on this and I've forgotten or missed it.)	Please note that we were referring to study arms (not studies). Also note that we cannot distinguish between lack of use and poor reporting of co-medications. We have clarified this in the text.

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Commentator & Affiliation	Section	Comment	Response
TEP #1	Executive Summary	ES-8: Note that the title and legend of figure ES-1:3- ??? are obscured	We apologize for any inconvenience caused by this typesetting mistake. We have made sure that the title and legend are clearly visible in the revised version of the report.
TEP #1	Executive Summary	ES-12 Line 34: Reword the first phrase on this line	We have rephrased.
TEP #1	Executive Summary	ES-14 Line 22: “modest (30-50%) change in odds in either direction”. That is a VERY useful finding – and presumably reassuring to those who might want to abandon OMBP.	Thank you. This result is based on inspection of the credible intervals for the association of OMBP with each of the outcomes of interest. This has been clarified in the executive summary and main text.
TEP #1	Executive Summary	ES-14 Line 22: Can you add a calculation for the potential absolute differences in a few key outcomes? Given the small event rates, the absolute diffs may be pretty tiny. I realize you would have to go beyond the ORs to make such estimates.	In the figures we have provided event rates (study-specific and overall) to give a sense of the absolute magnitude of effects. We have also provided power calculations that make direct use of the event rate information to estimate required sample sizes for different study designs. However, we have refrained from reporting absolute risk differences. First, absolute differences generally tend to be heterogeneous across studies. Second, as the reviewer suggests, using odds ratio meta-analysis results to derive absolute risk differences requires the specification of the baseline odds (and baseline event rates). Results at a given baseline rate are unlikely to transfer across populations and can be misleading.
TEP #1	Executive Summary	ES-18 Lines 6-7: Might you add how many more RCTs and NRCS you have included compared with the Cochrane review? Or give some sense of the increased number of pts included?	In the Discussion section (of the ES and the main text) we have provided a summary of the differences between our work and the Cochrane review.
TEP #1	Executive Summary	ES-18 Line 25: “three relevant non-English” but ES-5 line 38 mentions four relevant trials.	Thank you for noticing this typo! We have corrected the number.
TEP #1	Executive Summary	ES-19 Line 17: Change “remain” to “reveal” or “show”?	We have adopted the suggested phrasing.
TEP #1	Executive Summary	ES-19 Line 41: “meta-of existing trials”; Should it be “meta-analysis of existing trials”?	We have corrected this typo. Thank you.

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Commentator & Affiliation	Section	Comment	Response
TEP #1	Executive Summary	ES-19 Line 47: What kind of decision support tools would you be considering? Individual patient risk factors that might favor or disfavor OMBP? If so, you did not report any. Do you mean that individual level patient data might disclose some risk factors?	We have removed the recommendation for decision support tools since the evidence does not appear mature enough to support personalized decision-making.
TEP #1	Figures	Figs 3 and 4 are very interesting.	Thank you. No further response necessary.
TEP #1	Figures	Figure 9, on pg 30, has an incorrect title: it should (presumably) be Surgical Site Infections. Instead, you have copied the title of Figure 8.	Thank you for noticing this typo! We have used the correct Figure title.
TEP #1	Figures	Figure 10 precedes Figure 9. They (or their titles) should be reversed.	Thank you for noticing this typo! We have corrected the numbering of Figures 9 and 10.
TEP #1	General	I read mainly the Abstract and Exec Summary through page ES-20	Thank you. We appreciate your help in improving these sections.
TEP #1	General	A really impressive piece of work!	Thank you. No further response necessary.
TEP #1	General	Very meaningful and beautifully reasoned	Thank you. No further response necessary.
TEP #1	General	Addresses the practicalities, broad implications and limitations very well.	Thank you. No further response necessary.
TEP #1	General	You might want to include at the outset a table of abbreviations and their definitions, e.g. NRCS, MCMC, ROB	A list of abbreviations is provided at the end of the document, per AHRQ style requirements.
TEP #2	Introduction	No comments - seems fine	Thank you. No further response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Methods	I am unclear why the comparisons for Question 1 are stratified by the use of an enema, particularly when in 2 of the trials assigned to the enema comparison (Zmora and Bucher) only used an enema on patients undergoing rectal surgery with an anastomosis - the minority of patients included in these studies. The authors of the current analysis do not present a sufficient rationale for this approach. Given this, it is difficult to support a network analysis attempting an indirect comparison between no prep and enema only. Additionally in the 2 studies that did routinely administer enemas entirely different strategies were employed - so the group of studies assigned to the "enema" group were heterogeneous. I really question any indirect comparison of this group of studies to no prep	<p>In the revised report we have performed additional analyses, including analyses not stratified by the use of enema. Our conclusions did not change.</p> <p>Regarding the studies by Zmora and Bucher: we decided to include them with studies using enemas for all patients because enemas were used in patients for whom they are likely to have an effect (i.e. patients undergoing rectal surgery). This is consistent with the Cochrane report on the same topic. Further, we have performed analyses after excluding these studies and results were similar.</p> <p>The only additional assumption (compared to the standard meta-analysis approaches recommended by the reviewer) made by our "network meta-analysis" is the assumption of common variance (NB: we are assuming homogeneity of variances; not homogeneity of effects) between comparisons of OMBP vs. no preparation and OMBP vs. enema. As such, it can be thought of as a straightforward extension of the stratified pairwise analysis. This homogeneity assumption is useful to explore because the OMBP vs. enema subgroup of studies is extremely small (at most 4 trials are included for a given outcome). In such cases subgroup-specific estimates of between-study heterogeneity are unstable; and the "network" analysis can produce better estimates of heterogeneity (and consequently, better estimates of effect).</p>
TEP #2	Methods	I recommend an overall analysis comparing OMBP +/- enema to no OMBP +/- enema (vs the stratified analysis).	We have added results from these analyses for all outcomes.
TEP #2	Methods	If this stratified analysis is to be maintained, I question the inclusion of the Zmora and Buchner studies in the enema group - most patients in these studies did not receive an enema.	Please see above for reply to the same comment, These studies were subjected to sensitivity analysis. Their exclusion did not affect our conclusions.

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Commentator & Affiliation	Section	Comment	Response
TEP #2	Methods	The methods do not include a definition for "peritonitis or intra-abdominal abscess" - how were these outcomes assessed? Was this always how these outcomes were reported or in some studies were they reported separately? The Cochrane analysis includes peritonitis but does not include intra-abdominal abscess in this outcome. I think this is OK but given it is the one outcome demonstrating a statistical difference it is important that the reader understand this outcome with explicit definitions and reporting	We have provided details on outcome definitions in the Methods section of the revised report. The Cochrane report labeled as "peritonitis" the outcome that we (more accurately) termed "peritonitis/intra-abdominal abscess". This can be verified by examining the extracted data from studies included in both reviews. In passing, please note that the Cochrane report misinterprets "intention to treat" analyses and imputes missing data in an ad hoc way.
TEP #2	Results	The results are presented in a clear fashion and the documentation is extensive	Thank you. No further response necessary.
TEP #2	Results	Again, I have reservations about stratification of the results by use of an enema - I think this adds little and the enema comparison includes 2 studies where the minority of patients had an enema. I have reservations about presentation of the network analysis as the enema studies are entirely inconsistent wrt the type of enema used. The network analysis is presented in detail but is not a valid comparison. I do not think this should be included in this report.	Please see above for our reply regarding stratification by enema use.
TEP #2	Results	WRT stratification by location (rectal vs colonic) the authors state that only 1 outcome was routinely reported, anastomotic leakage. This would absolutely be the most relevant outcome to a clinician so it would be appropriate to present these results. I note that the recent Cochrane meta-analysis did report on anastomotic leakage stratifying colon and rectal surgery. I would therefore identify this as a deficiency of this report	This analysis has been added to the final report.
TEP #2	Results	There seem to be a number of studies included in the Cochrane meta-analysis that were not included in this report. This may be reasonable, but it would be useful to be quite transparent about the differences. It is challenging to go through all the excluded studies to understand the differences - perhaps a section could be included explicitly stating the differences between the studies included in the 2 meta-analyses	We have expanded somewhat our description of the differences between our work and the Cochrane report. We believe that additional information on the Cochrane report would place undue emphasis on analyses performed with methods that do not incorporate the uncertainty in the available evidence.
TEP #2	Results	The results are presented in great detail for the comparison of alternate active strategies, yet at the end of the day there is little to be concluded from this analysis.	We believe that this is a reflection of the limitations of the evidence base, despite our best efforts.
TEP #2	Results	The comparison of inpatient and outpatient prep is of purely historic interest - this is not relevant to current practice.	We have streamlined the information provided in the ES on this comparison. We have reached the same conclusion as the reviewer.

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Commentator & Affiliation	Section	Comment	Response
TEP #2	Discussion	No studies were conducted in the US, however there are no system differences that I can anticipate that would create any challenge generalizing these results to the US population.	We agree. We have concluded that the evidence in applicable to the U.S. setting.
TEP #2	Discussion	Given that the authors are proposing the need for another RCT based on this meta-analysis, it would be useful for the authors to also provide an estimate of the sample size for such a trial. Based this meta-analysis, to design such a trial one would have to hypothesize a very small expected differences between the OMBP and control groups (as although the confidence intervals for the parameter estimates are low, most estimates are close to 1). Essentially the trialist designing such a study would be attempting to prove no difference and the numbers needed to recruit would actually be huge, particularly as the authors are proposing the trial be powered to detect a difference in MORTALITY, a rare event. From my crude calculations, to demonstrate a 40% relative risk reduction in mortality in this group would require randomization of 4,569 patients per arm with a 2-tailed alpha of 0.05 and power of 0.8. This risk reduction however would not be consistent with the findings of the meta-analysis - the pooled OR for mortality is 0.94. To test a 20% relative risk reduction (a more realistic estimate) at a power of 0.9 would require randomization of over 27,000 patients per arm.	We have provided some information regarding the design of future studies. The reviewer seems to be overlooking the potential for using a non-inferiority design, with a sufficiently narrow non-inferiority margin.
TEP #2	Conclusion	Given the lack of implementation of decision aids that have been proven effective for important decisions such as surgical options for breast cancer, creating a decision aid for the use of mechanical bowel prep would seem a waste of resources. It highly unlikely that clinicians would use such a decision aid with their patients.	We have removed the recommendation for decision analysis or decision aids.
TEP #2	Figures	The figures for this section are challenging to interpret.	We have simplified the presentation of data in the ES.
TEP #2	Appendix	The presentation of analyses of historic relevance detract from the document - perhaps the most of this evaluation could be relegated to an appendix, given that it is not relevant to current practice	Some of the more detailed information has been confined to the main text of the report.
TEP #2	General	The key questions are explicitly stated and are clinically meaningful	Thank you. No further response necessary.
TEP #3	Introduction	The background is detailed and well stated.	Thank you. No further response necessary.
TEP #3	Methods	Clear, appropriate, logical.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
TEP #3	Results	Considering the profound heterogeneity of the data collected and the variety of conclusions published to date, this was a huge challenge that I believe the authors handled extremely well.	Thank you. No further response necessary.
TEP #3	Discussion	Well-done.	Thank you. No further response necessary.
TEP #3	Discussion	I would have preferred a more forceful denunciation of the practice of OMBP considering, as implied by the authors, that it was based on a reasonable but probably incorrect guess many decades ago and became inviolable dogma without ever having proven itself useful. Nevertheless, I understand the reason based on the statistical analysis presented that the authors chose to state their conclusions in such an understated manner. The understated conclusions will likely allow proponents and opponents of OMBP alike to use the data to confirm their particular bias. My own conclusion (that the lack of a clear benefit after review of so many albeit heterogeneous studies supports the null hypothesis) is probably evidence of my own bias.	We think that the key message of our analyses is that of overwhelming uncertainty for many key clinical outcomes.
TEP #3	Figures	The graphs and tables are clear.	Thank you. No further response necessary.
TEP #3	General	This is an excellent and very thorough review of an immensely important topic.	Thank you. No further response necessary.
TEP #3	General	Although the principal conclusion might very well be the tired cliché that making sense of the surgical literature and drawing meaningful conclusions that can help the daily practitioner amount merely to an exercise in frustration, I believe the lack of evidence found in favor of either approach (OMBP or no OMBP) supports the concept that OMBP is most likely useless as designed for most patients. The next step for us is to devise better studies that might identify certain operations in certain patients under certain circumstances in which there might be a benefit.	We agree and have provided recommendations about the design of future studies.
TEP #4	Executive Summary	I think the Executive Summary could benefit from a line/reference in the methods sections regarding how bias was assessed.	This information is provided on page 4 of the ES.
TEP #4	Introduction	The introduction or background is very thorough, thoughtful and informed.	Thank you. No further response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Introduction	I was impressed by the clear identification of Key Questions.	Thank you. No further response necessary.
TEP #4	Introduction	I feel this will be very helpful for the reader and researcher wishing to design another study.	Thank you. No further response necessary.
TEP #4	Introduction	Dr. Cindy Kin presented an abstract at the ASCRS in May referencing the actual cost of a leak which is interesting background information for costs which would underscore how important this issue is if one or the other decreases leak rates.	We have not provided information on the cost of specific outcomes given that this was not covered by the review. We mention though that additional surgeries and other interventional approaches may be needed if complications arise.
TEP #4	Methods	Inclusion and exclusion criteria are clear and justifiable.	Thank you. No further response necessary.
TEP #4	Methods	Search strategies seemed clear and logical.	Thank you. No further response necessary.
TEP #4	Methods	Definitions were understandable and diagnostic criteria for outcomes clear and appropriate.	Thank you. No further response necessary.
TEP #4	Methods	I cannot comment on appropriateness of statistics.	Thank you. Please note that a statistical reviewer provided a critique focusing on the statistical methods. Please see above for our replies to his comments.
TEP #4	Methods	I felt the explanation (of how bias was assessed) in the full report was valuable and informative.	Thank you. No further response necessary.
TEP #4	Results	The results section was clear with appropriate and adequate tables.	Thank you. No further response necessary.
TEP #4	Results	The messages are applicable.	Thank you. No further response necessary.
TEP #4	Results	I don't believe any studies were overlooked.	Thank you. No further response necessary.
TEP #4	Discussion	As with the other sections, I felt major findings were clear, recommendations for future research were clear and stated in such a manner as to help future efforts.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
TEP #4	General	I believe the report is clinically meaningful.	Thank you. No further response necessary.
TEP #4	General	The target population is well defined as is the audience.	Thank you. No further response necessary.
TEP #4	General	The key questions have been formulated clearly and defined as in no other review.	Thank you. No further response necessary.
TEP #4	General	Very well structured and organized and useful for directing future research efforts and policy or practice decisions.	Thank you. No further response necessary.
TEP #5	Executive Summary	The key questions are clearly defined - did you want to include surgical approach as a subpart of the key question #1?	Thank you for this comment and suggestion. In this report, a decision was made that Key Question 1 should reflect one particular subgroup analysis (by anatomic location) because we thought that this is the key modifier of OMBP effectiveness. Although the effect of "surgical approach" on OMBP effectiveness was considered to also be of interest (and was listed in our protocol as a pre-specified analysis of effect modification), we did not think that it should be part of the Key Questions (i.e., we thought it is less critical than anatomic location of surgery). Given the very limited evidence identified regarding difference between laparoscopic vs. open surgery, we think that that our decision was justified.
TEP #5	Introduction	Consider adding a few points to the discussion as to why the location of surgery (e.g. right colon vs. left colon vs. rectum) or surgical approach (laparoscopic versus open) are clinically important reasons to consider giving (or not giving) OMBP or may influence studied outcomes (e.g. SSI, anastomotic leak).	We have provided some Background information in the Introduction section of the revised report and have mentioned this issue in the Discussion section as well.
TEP #5	Methods	Inclusion/exclusion criteria are appropriate and explicitly stated.	Thank you. No further response necessary.
TEP #5	Methods	No issues with search terms or statistical methods.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
TEP #5	Methods	Consider commenting on how got from 8759 publications to 804 full text review articles. Were the remaining articles screened by title/abstract? Do we know why they were excluded (e.g. non-surgical studies)?	We have provided the requested information in the first section of the Results.
TEP #5	Results	Consider adding comment to results that you were also unable to evaluate effects of OMBP separately by surgical approach (laparoscopic versus open).	We have provided the requested information in the Results section and have discussed its implications for future research in the Discussion section of the revised report .
TEP #5	Results	It is difficult to clinically separate the outcomes of anastomotic leak, intraabdominal abscess, and peritonitis. For example, some patients with anastomotic leak may also have intraabdominal abscess and peritonitis. Other patients may manifest their anastomotic leak as an intraabdominal abscess but NOT have peritonitis. Does it make sense to group these 3 outcomes as one? Also wound infection and surgical site infection mean the same thing to me - should these also be combined into one outcome?	We generally relied on the outcome definitions of included studies. We cannot combine anastomotic leak, abscess and peritonitis, because it was not clear in the reviewed studies whether events occurred in independent or (partially) overlapping populations. We have discussed the implications of inconsistent reporting the Final Report.
TEP #5	Discussion	I think the key findings and strengths/limitations are clearly stated.	Thank you. No further response necessary.
TEP #5	Discussion	The author make a good argument as to why further well-designed studies are needed to better evaluate the comparative effectiveness of OMBP.	Thank you. No further response necessary.
TEP #5	Conclusion	Unfortunately the conclusions are limited due to the quality and detail of the previously published studies.	We agree with this point. We hope that our work highlights the uncertainties in the available evidence and can be used to inform the design of future research studies.
TEP #5	General	This is a very well written report on the important topic of oral mechanical bowel preparation in elective colorectal surgery.	Thank you. No further response necessary.
TEP #5	General	Report is well structure and organized.	Thank you. No further response necessary.
TEP #5	General	I think the sections on evidence gaps and future research are critical to moving the field forward and identifying the need for a well-designed trial to help answer these important questions.	Thank you. No further response necessary.
TEP #6	Executive Summary	The key questions are appropriate and explicitly stated.	Thank you. No further response necessary.

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Published Online: April 30, 2014

Commentator & Affiliation	Section	Comment	Response
TEP #6	Executive Summary	I disagree with your inclusion criteria. There is Level I evidence from RCTs. Thus, although the non-randomized studies were not combined with the RCTs, I wonder why they were included.	The existence of RCTs is not adequate reason to disregard observational studies. Often RCTs do not explore all outcomes of interest, particularly adverse events. Furthermore, given that the outcomes of interest to this report are rare, observational data may offer the only reasonable method for evaluating effectiveness. Finally, we were careful to distinguish between observational studies and RCTs in our interpretation of their results.
TEP #6	Introduction	Good	Thank you. No further response necessary.
TEP #6	Methods	Having said that, this meta-analysis and systematic review is over the top. I have a strong clin epi background and have done meta-analyses but I had trouble following all of the statistical analyses.	We have tried to simplify the Executive Summary. We think that complex data require advanced methods to yield meaningful answers, particularly with respect to the uncertainty of the underlying evidence.
TEP #6	Methods	Fine-cannot discuss the statistical methods because I cannot understand them	Thank you. A statistical reviewer has reviewed the analysis methods. Please see above for our replies to their comments.
TEP #6	Methods	Also, there were studies dating back to 1972 and I wonder why you did not limit your search to say "the modern era" and only included the more recent studies.	Unfortunately, the "modern era" is a rather elusive concept. The implementation of changes in care does not happen at a uniform pace across healthcare systems. Furthermore, in randomized trials, both treatment arms are exposed to the same (non-randomized) components of care, rendering bias unlikely. Nonetheless we have performed regression analyses with year as a covariate to explore whether the effect size of OMBP has changed over time (these analyses assess effect modification over time). These analyses did not reveal an association between year of publication and estimated effect size.
TEP #6	Methods	Surgery has changed a lot since the 1970s and I don't think some of the regimens are relevant and the results also may not be relevant because of the changes in antibiotics, surgical technical, post operative care as well as potentially the presence of more resistant bacteria in the gut etc etc.	We agree that there have been many changes over the period covered by the included studies. This is one of the reasons we did not synthesize studies comparing alternative active OMBP strategies (older) with studies comparing OMBP versus no-OMBP (more recent).

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Commentator & Affiliation	Section	Comment	Response
TEP #6	Results	I think the key messages get lost because there are so many analyses.	We have streamlined the Executive Summary to clarify the message.
TEP #6	Conclusion	I disagree with your conclusions. I think you have shown that overall that giving a OMBP does not improve outcome. I do not think you have to prove that they are the same. Thus, I think your conclusions are too conservative. We live in a real world and this evidence is a lot better than dredging administrative data for treatment effectiveness!!	We respectfully disagree with this interpretation of our work. We believe that there is substantial uncertainty in the available evidence and this has been highlighted by our analyses. The evidence was often too sparse to support stronger conclusions.
TEP #6	Conclusion	Who is going to pay for this large multicentre trial that you think needs to be performed??? If someone will fund another trial, please let me know-I would love to get that funding and would be pleased to do it!	We have provided details about the sample size requirements for such a trial. We believe that the required sample size is not prohibitive (even for a small size consortium) given the wealth of information that could be obtained. Unfortunately, our EPC does not provide advice on funding strategies.
TEP #6	Conclusion	As above, I think the conclusions are too conservative-I think the conclusion should be OMBP (overall) is not superior!	Please see our replies to the comments listed above.
TEP #6	General	This is very comprehensive. I am not sure who the target audience is but if it is the average clinician they will have a hard time reading this. There is just too much information and too many analyses.	Thank you. No further response necessary.
TEP #6	General	Thanks for the opportunity to comment. Despite my negative comments, I admire the work that has been put into this review.	Thank you. We hope that we have adequately addressed your comments.
TEP #7	Executive Summary	The key questions were relevant and focused.	Thank you. No further response necessary.
TEP #7	Executive Summary	I find the text in the executive summary much easier to read for the non-expert on meta-analysis.	Thank you. We have tried to streamline the executive summary even further.
TEP #7	Introduction	The introduction provides an excellent overview of the OMBP for colorectal cancer and discusses the uncertainties on this topic.	Thank you. No further response necessary.
TEP #7	Introduction	The key questions are also very relevant.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
TEP #7	Methods	The methodology appears rigorous taken into consideration the limitations of the data. However, I am a clinician with no training in methodologies and I am not in the position to make an in-depth review of the methodology.	Thank you. Please note that a statistical reviewer has also provided a critique. Please see above for our replies to his suggestions.
TEP #7	Methods	One of the limitations of the study (I would say of the data used in this meta-analysis) is that the enrolment period for the RCTs is quite long. Many things have changed in perioperative care and surgical technique over such a long period. This may have some influence in the results. As some of the complications are now less frequent that were years ago, studies that were positive in the past may be negative now. Unfortunately the results were predictable for anyone interested on this topic.	We agree that there have been many changes over the period covered by the included studies. This is one of the reasons we did not synthesize studies comparing alternative active OMBP strategies (older) with studies comparing OMBP versus no-OMBP (more recent).
TEP #7	Results	The results section contains a great deal of details	We have streamlined the Results section of the Executive Summary to focus on key points.
TEP #7	Results	The outcomes chosen are well defines and all relevant.	Thank you. No further response necessary.
TEP #7	Results	The difference in pelvic abscess between OMBP and no prep, come mainly from 2 relatively large European/Scandinavian studies has been previously noticed, but is clearly presented in this study.	Thank you. No further response necessary.
TEP #7	Results	The network metaanalysis was new to me, but I found informative.	Thank you. No further response necessary.
TEP #7	Conclusion	I also concur with the major gaps in the published evidence, but probably I am less optimistic about the success of future RCT. As stated by the authors of the study, the quality and the size of the randomized controlled trials and the nonrandomized comparative studies currently available is not that good, and therefore it is impossible to reach a conclusion in way or another. While I agree with the author's statement that the gap of knowledge persists, I am not so optimistic about the feasibility of a large study that will fill that gap. Considering the measurable are infrequent (anastomotic leak, pelvic abscess, etc.), and that the study will need to be stratified by anatomical segment, the sample sizes will need to be large. Although there seems to be equipoise around this issue and the number or colectomies performed every year is large, the fact is that most surgeons have a strong opinion in one direction or the other and many will not be willing to randomize patients to a large prospective trial.	In the Discussion section we have provided power calculations for a future large-scale randomized comparison, for establishing superiority and non-inferiority.

Commentator & Affiliation	Section	Comment	Response
TEP #7	Conclusion	Part of the problem is also related to the fact that the available literature does not capture other issues that are relevant to the surgeons treating these patients, such as the ability to perform a colonoscopy during a laparoscopic colectomy, or the easier handling of an empty colon.	We agree that the trial literature does not adequately capture all contextual issues. However, given the large uncertainty regarding important patient relevant outcomes, we have refrained from suggesting future research on (patient or physician) preferences and contextual factors.
TEP #7	Conclusion	The conclusion is reasonable and based on the evidence provided.	Thank you. No further response necessary.
TEP #7	Conclusion	The limitations are also properly discussed.	Thank you. No further response necessary.
TEP #7	Conclusion	Overall I think this is a rigorous work that summarizes well the current status with this topic.	Thank you. No further response necessary.
TEP #7	Figures	The tables and figures are informative	Thank you. No further response necessary.
TEP #7	Figures	The rank probability took a bit longer to understand (Fig 12), but also provided interesting information.	Thank you. We have provided a more detailed explanation of the graph in the corresponding legend.
TEP #7	General	In my opinion this is an excellent review of a clinically relevant topic.	Thank you. No further response necessary.
TEP #7	General	The authors did a good job reviewing and interpreting the literature.	Thank you. No further response necessary.
TEP #7	General	The quality of the writing is excellent.	Thank you. No further response necessary.
TEP #7	General	The report is long and detail, but very thorough.	Thank you. No further response necessary.
TEP #7	General	I think it is the ultimate review on this topic.	Thank you. No further response necessary.

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Commentator & Affiliation	Section	Comment	Response
TEP #7	General	It should be made available to anyone interested in this topic.	The full text of the Final Report will be freely available through the Effective Healthcare Program's website: http://www.effectivehealthcare.ahrq.gov . We will also disseminate our findings as an article in a surgical peer-reviewed journal.