Project Name: Antiemetics
Project ID: CANMO509

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	We very much appreciate the opportunity to review this report, "*Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy*" prepared by the Oregon Evidence-based Practice Center.	Noted.
2	General	The Technology Assessment Report on antiemetic drugs for nausea and vomiting associated with chemotherapy or radiation therapy is comprehensive and well written. The three questions addressed are clinically relevant and clearly impact on daily practice. I am in agreement with most of the conclusions. I do not believe a compelling case has been made for several conclusions, however, and I will cite additional references which hopefully may illustrate my points	Noted.
3	General	This is an important topic, as nausea and vomiting is one of the most common side effects of chemotherapy and radiotherapy. In addition, this is the side effect most likely to occur immediately during or soon after receiving therapy and the one that patients and the general public often associate with anti-cancer therapy. Fear of nausea may lead patients to forego helpful therapies and severe nausea and vomiting has an adverse effect on patients' quality of life (QOL) and may lead them to abandon helpful therapies.	Noted.
3	General	In addition, the categories of anti-nausea drugs that have become available in the past two decades are generally felt to be effective and are somewhat costly. Knowing how best to use these medications will enhance the care of cancer patients, improve QOL and should lead to cost-effective care.	Noted
3	General	There was a specific need to address the use of antiemetics in the elderly. However, the reviewers correctly concluded that	"in adults" added to title. Kept radiation in title as a reflection of

		the currently available data cannot assure efficacy and safety in those older than 65. There is no attempt in this report or study to address the use of these medications in children or adolescents. Therefore, I recommend that the words 'in adults' be added to the end of the title. Also, since the reviewers were unable to find enough data regarding the use of these medications with radiation to evaluate them in that setting, one wonders why the word 'radiation' should remain in the title.	the objectives of the review.
3	General	Overall, the report is well-written and easy to read. The data and conclusions are clearly presented throughout. The report should achieve improved knowledge and care in adult patients who need moderately or severely emetogenic chemotherapy. No conclusions can be stated regarding radiation.	Thank you.
2	Introduction/Background	The oral formulation of palonosetron, although approved for use, is not currently available in the United States	Footnote added to Table 1
3	Introduction/Background	The introduction addresses the currently most commonly used anti-emetic regimens that are FDA-approved. Very little mention is made of medications that were commonly in used prior to 1991, when ondansetron was FDA approved and entered the marketplace. This is appropriate, as older regimens were certainly less effective and should not be used in the modern era. However, might it be better to clearly state early in the report that only 5-HT3 antagonists, aprepitant and steroids are being considered for this report.	The introduction has been revised to indicate the history of drug development in this area more clearly – including the fact that older drugs were used but with inadequate response and intolerable side effects. The "Purpose of the Report" section states that the focus of the report is on 5-HT3 antagonists, aprepitant and steroids. We moved this section to earlier in the report, for more clarity.
3	Introduction/Background	The section entitled 'Purpose and Limitations of Systematic Reviews' is well written and important, as many practitioners (medical and public health) may not be familiar with the reviews and the technical terms that such reviews use. No changes are suggested. Under 'Purpose of the Report', there is no mention of whether children and adolescents were included in the previous report. This information would be helpful. The 'Key Questions' section is fine.	Added clarification about scope of previous DERP report

1	Executive Summary	The executive summary of the document is readable and conveys the completion and findings of this systematic review succinctly.	Thank you.
3	Executive Summary	The executive summary is well written and faithfully represents the contents of the full report. Readers who need quick information regarding the contents and conclusions of the study will be able to glean the needed information from this summary.	Thank you
2	Methods	Standard antiemetic outcomes were evaluated. A major limitation of the analysis, however, is to include outcome data only for the acute and delayed phases but not for the entire study period. In nearly all the studies cited, complete response during the 120 hours after chemotherapy administration was the primary endpoint. The separation of response into discrete acute and delayed periods, while of interest to antiemetic aficionados is of little interest to patients. They simply wish to know whether they will experience nausea or vomiting during the period of risk after chemotherapy (best encompassed by the 120 hour time period). I would recommend including this endpoint.	Overall study period data added
1	Methods	Inclusion and exclusion criteria (pgs 16-17; 65): Further explanation of these is required, particularly category 6 of wrong study design. Insufficient information is provided for the list of excluded trials. For example, the Abal*i et al.*, Cancer Investigation 2007, pg 65, trial should meet the pre-specified inclusion criteria (the tropisetron arm could have been excluded and other analyses reported).	Agree, Clarification added. Abali 2007 was excluded due to being a comparison of all-IV vs all-IV
1	Methods	An additional criterion should consider drug doses in a given trial. Studies which employ doses which are not consistent with FDA-approved labels should be excluded, similar to the exclusion of non-FDA approved therapies. Table 1 (pg 11) could be expanded to include the range of doses approved by the FDA for each drug considered in this systematic review.	Dosage was considered within our interpretation of the results, rather than as an eligibility criterion. Added appendixes of FDA-recommended dosages
1	Methods	Search terms (pg 52): Suggest consider inclusion of the drug categories, 5-HT3 serotonin receptor antagonists and Neurokinin-1 receptor antagonists, rather than the drug names alone.	Our experience in conducting searches for the original DERP review and for its update has not indicated that this approach is

			necessary for this particular drug group.
1	Methods	Additional sources: Suggest consider additional sources beyond the published medical literature including presentation and posters from the following meetings: Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), European CanCer Organisation, European Society for Medical Oncology (ESMO), and American Society for Therapeutic Radiology and Oncology (ASTRO). ASTRO would be particularly useful source for studies on radiation-induced nausea and vomiting.	Due to our concerns about potential for outcome reporting bias and insufficient methodological reporting detail, our current policy is to exclude conference proceedings.
1	Methods	Emetic risk (pg 16): Verification of emetic risk in future reports is suggested. Inconsistencies between author designation and current risk stratifications schemas were noted. Notably, the emetic risk classification schema was revised (http://www.mascc.org/mc/page.do?sitePageId=88041, accessed 04/30/2010) at the MASCC 2009 meeting. As well, the draft update of the ASCO evidence-based guideline for antiemetic therapy for cancer patients also includes a revised emetic risk classification schema.	No inconsistencies identified between emetic risk in included trials and MASCC 2009 revision. Added MASCC 2009 revision as source for emetic risk classification
1	Methods	Collation of findings for the different questions (two or three therapy treatment arms) is described without separating trials based on emetic risk; either high or moderate. Studies may be combined or compared inappropriately by failing to consider such. Results may then be extrapolated to cover an array of emetic risk categories rather than considering direct evidence for a given risk category.	Comparisons of all-oral regimens were restricted to trials of moderate emetic risk. Whereas, comparisons of mixed regimens were restricted to trials of high emetic risk, with one exception. In Chiou 2000, emetic risk was high for 57% and moderate for 43%. Added clarification to Executive Summary and Summary Table to better emphasize this.
1	Methods	Outcome Measures (pg 17): The most meaningful outcome measure included is total control, which includes effects on nausea. The importance of this endpoint, which represents a true antiemetic effect, is paramount in making, determinations about strength of evidence. This is equally important when	We agree and have emphasized its importance in this review

		making coverage determinations. A failure to effectively control nausea, in addition to emesis, considering the antiemetic therapies available represents strides lost in the battle to control this symptom with significant impact on quality-of-life.	
1	Methods	Intention to Treat (ITT) Analyses: Suggest utilization of the ITT definition published within the report (pg 45), which includes all patients randomized. For those non-ITT analyses, would suggest specification that an analysis is actually a modified ITT (mITT) to increase transparency.	As there exist multiple and variable definitions for modified ITT, to avoid ambiguity, we have hesitated to adopt use of this terminology.
1	Methods	Additionally, a "very small number" is not defined. The language in the data abstraction section (pages 17, 18) does not indicate when ITT was calculated by the authors. This section is difficult to interpret; it is not clear when ITT was calculated or when a "very small number of patients" were not included. In those cases when it could not be calculated because data was lacking, indicating that results are per-protocol can also increase transparency. This information is particularly critical for readers considering results for the numerous meta-analyses.	We define "very small" as ≤ 5% and added this clarification. Also added clarification that we would note cases where we calculated intention-to-treat results when only per-protocol results were available. There were no occasions for such calculations in this review.
1	Methods	Data Synthesis (pg 20): Suggest that meta-analysis is first conducted with fixed-effects model to determine whether a random-effects model is necessary.	We adhere to the guidance issued by the EPC program which recommends against choosing a statistical model based on the significance level of a heterogeneity test and, instead, recommends routine use of random effects models.
1	Methods	An increased I^2 does not necessarily indicate that a random-effects model is required, particularly in trials with homogeneity. It may, alternatively, suggest that factors not accounted for in stratification mediate outcomes.	See above response.
3	Methods	The methods used for this review are clearly presented in this section. However, I find it interesting that the reviewers state that they went back to 1966 (perhaps this is just because it is the lower limit of the MEDLINE® database), when the review really is limited to relatively new (< 2 decades) medications (with the exception of steroids).	Yes, the start date of our search reflects the lower limit of the MEDLINE® database

3	Methods	The definitions used for emetogenic potential of chemotherapy regimens are clearly presented, and the effectiveness and harms outcomes are also clearly presented.	Thank you.
2	Results	Key Question 1: All-oral regimens -Comparison of regimens with and without aprepitant • Two studies are cited, Warr et al and Yeo et al.Both are described as “fair-quality” studies. To rate the quality of these studies as equivalent makes little sense to me. The Warr study with 866 patients is properly sized to address the question of interest. The other trial is woefully underpowered to address the primary endpoint.	The impact of sample size is considered to be distinct of risk of bias and is evaluated in the form of “precision” in our grades of the strength of the evidence.
2	Results	Key Question 1: All-oral regimens -Comparison of regimens with and without aprepitant • Recently, another large (848 patients) phase III trial (Rapoport et al) has been published in a MEC population with an identical study design to the Warr trial. Unlike the Warr trial in which the aprepitant regimen was better than the control regimen in the acute and overall periods only, in the Rapoport trial the addition of aprepitant improved outcome across all the phases(acute, delayed, overall). The combined weight of both the Rapoport and Warr trials should improve the level of evidence to a high level of confidence that an all oral three-drug regimen with aprepitant is superior to an oral two-drug regimen without aprepitant in achieving complete response in the overall study period.	This recently published study was added.
2	Results	Key Question 1: All-oral regimens – comparisons of regiments of a 5-HT3 antagonist plus a corticosteroid, without aprepitant • Essentially no data. One very small randomized trial.	We agree.
2	Results	Key Question 1: All-oral regimens compared to all-injectable regimens • No data	We agree.

2	Results	Key Question 1: Comparison of mixed oral and injectable regimens with and without aprepitant • I again do not understand the quality rating for the trials in that only one trial was rated of good quality. I agree with the conclusions. The strength of evidence is very high that mixed oral and injectable regimens with aprepitant are superior to those without aprepitant.	None of the 7 trials of mixed oral and injectable regimens that compared the addition of aprepitant to dual therapy provided sufficient detail to determine adequacy of allocation concealment. According to our quality assessment methods, unless allocation methods can be verified as adequate, the highest rating that can be given is "Fair". Schmoll 2006 changed to Fair for this reason. Added explanation of rating.
2	Results	On p 27 the statement is made that no trials reported on the ability to tolerate sequential chemotherapy sessions. This is not true. Both the Hesketh[33] and Poli-Bigelli[35] trials allowed patients to remain on assigned treatment arms during subsequent cycles of cisplatin-based chemotherapy. The multi-cycle data was reported by de Wit et al in the EJC in 2004. I will forward the reference. In addition, multi-cycle data is also available from the Warr[27] trial as well (Herrstedt et al Cancer 2005). I will forward this reference as well.	Added.
2	Results	Key Question 1: Comparison of mixed oral and injectable regimens of a 5-HT3 antagonist plus a corticosteroid • Very little data. Agree with conclusions.	No changed needed
2	Results	Key Question 1: How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time? • Definitive evidence demonstrating that a single day aprepitant regimen has comparable effectiveness to a multi-day regimen has not yet been published. Neither the small pilot trial of Herrington32 nor the randomized phase II trial of Navari34 was powered to answer this question. Further support for the concept that single day NK1 receptor antagonist dosing can achieve comparable efficacy to multi-day NK1 receptor	Agree. We rated the strength of this evidence as moderate, due to the imprecision of effect estimates caused by the small sample sizes in these trials. No change needed.

		antagonist is provided by the report of Grunberg et al in Lancet Oncology 2009 detailing a large phase III trial with the NK1 receptor antagonist casopitant. The manufacturer of caospitant, GlaxoSmithKline has decided not to pursue a regulatory filing with this agent. I will forward this reference.	
3	Results	Key Question 1: • In section A, there is a discussion of 2 studies that compare a 2 drug regimen with ondansetron and dexamethasone to a 3 drug regimen that adds aprepitant. The reader must look at several tables and the references to confirm that both are randomized clinical trials. Clarification that these were randomized clinical trials with the simple insertion of the word 'randomized' in the first sentence would be helpful and allow the reader to focus on the data and results, rather than chasing down this information. Also, similar to my comments regarding table 4 (see below), in the QOL paragraph on p 23, one must infer that the order of outcomes is 3-drug vs. 2-drug. It seems that this is likely standard throughout the manuscript. If so, it should be more clear. The last paragraph in section A is clear.	Both changes made.
3	Results	Key Question 1: • In section C, please point out that the Evidence tables can be found in which appendix (G).	Added
3	Results	Key Question 1: • On page 25, there is a typo: in the last line before table 6, the word should be 'significant'.	Corrected
3	Results	Key Question 1: • The quality of life paragraph on page 27 is important and may warrant a subheader.	No change made; While quality of life is very important to patients and clinicians alike, this was only a brief report on quality of life and we felt it did not warrant adding an additional level of subheading.
2	Results	Key Question 2: Safety • Agree with conclusions	Noted.

1	Results	Key Question 2C, pg 29 • Review of the question indicates that relevant trials should compare therapies given 48 hours following chemotherapy delivery versus those given for over less than 48 hours. Antiemetic agents are delivered prior chemotherapy (generally ranging from 60 to 30 minutes before administration). Therefore, agents delivered before chemotherapy administration for three consecutive days period would fall within this 48 hour limit. Alternatively, agents delivered following chemotherapy over three days would fall into the beyond 48 hour category.	Agree
1	Results	Key Question 2C, pg 29 • The Herrington 2008 publication in Cancer does not compare these two sorts of regimens. The study design evaluates one day of aprepitant compared to three consecutive days; study therapies are all delivered before administration of chemotherapy. As such, both regimens are within the 48 hour time limit.	Agree. Removed Herrington 2008.
3	Results	Key Question 2: • The relatively short section on 'harms' is clear and concise. The message is that these medications are relatively well tolerated and that the evidence for significantly different side effects from differing regimens is currently lacking.	Thank you
2	Results	Key Question 3: Applicability of the evidence to patients age 65 and older? • Retrospective analyses assessing predictive factors for emesis have suggested that patient age may be relevant with younger patients experiencing more emesis than older patients. One of the earliest reports in this regard was by Pollera and colleagues in 1989. (see ref 6 from the NEJM 2008 review by Hesketh). • Although definitive information on the impact of age is not available as age has never been a stratification	We have cited the Pollera paper to indicate that it is known that older patients have lower rates of nausea and vomiting. The publication in J Support Care Cancer did not come up in our Medline searches, we appreciate this being brought to our attention and have added it, along with additional unpublished data

		factor in antiemetic trials, a recent analysis of predictive factors for emesis published by Hesketh et al (J Support Care Cancer 2009) strongly supports the conclusion that patients over age 65 also benefit from the addition of aprepitant. In this analysis of the combined data set from the two pivotal phase III trials of aprepitant with highly emetogenic chemotherapy, 285 (28%) of the total 1023 patients were over age 65. The complete response rate was significantly greater for the aprepitant-containing arm than the active-control arm, regardless of age.	submitted by Merck regarding the 2 trial from which data were pooled in this analysis, as well as others. Our conclusions have changed based on the new evidence.
2	Results	Key Question 3: Is there evidence of disparate effects on gender? o I do not agree with the conclusion that there is a low level of evidence that gender is a relevant factor in defining antiemetic outcomes. Early on, there was widespread recognition that female gender was an important predictive factor for antiemetic outcome, with women consistently having more nausea and vomiting than men with the same emetic stimulus. See references 6-9 from the Hesketh 2008 NEJM review. An analysis of the combined database from the two pivotal phase III trials of aprepitant with highly emetogenic chemotherapy by Hesketh et al43 again demonstrated significantly worse outcome in the control arms in women compared to men. Of note, for the first time the significant difference by gender was negated with the addition of aprepitant in the investigational arms, suggesting an even greater benefit with the addition of aprepitant in women compared to men. In my opinion the reports conclusions on p 32 that "further studies are highly likely to change these findings" are misleading and incorrect.	To introduce the discussion of comparative effectiveness differences in women versus men, we have added reference to the known difference between genders in nausea and vomiting. The publication in J Support Care Cancer did not come up in our Medline searches, we appreciate this being brought to our attention and have added it, Our conclusions have changed her also, but both are focused solely on the comparisons between treatment groups, such that analyses that do not take treatment group into account are not as relevant.
2	Results	Key Question 3: Is there evidence of disparate effects on race? o Agree	Noted.

2	Results	Key Question 3: Are certain groups more likely to receive one treatment over another , due to prescription trends in a geographic region, socioeconomic status, health insurance coverage, etc.? o No good information	Noted.
3	Results	Key Question 3: The relative lack of data on the effectiveness and side effects of these regimens in those older than 65 is unfortunate and clearly comes across in section A on page 31. I think that the concluding sentence, that presumes that adding aprepitant in all age groups is superior but may be overturned as evidence is accumulated, is correctly stated. Similarly, the concluding statement about differences across gender differences on page 32 is also correctly stated. It is unfortunate that studies have enrolled insufficient minorities for there to be data sufficient to analyze differences across races and ethnic groups.	Noted
1	Results	The Navari trial, alternatively, does compare regimens as described in key question 2C. Arm A includes five days of aprepitant, Arm B includes one day of aprepitant, and the third arm is a placebo comparator. However, The Navari trial includes a non-approved dose of aprepitant (original, FDA-approved label for Emend®; http://www.accessdata.fda.gov/scripts/ cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory, accessed 4/26/2010). The dose included in this trial is over three times the FDA-approved dose (125mg day one, 80mg days two and three). Moreover, this study was one of a number of dose-finding efforts completed by the manufacturer prior to approval of this agent. Recommend exclusion of this trial from consideration throughout the entire report. It was also included in the analysis of aprepitant use (two vs. three drug regimens); this study is not appropriate for pooling in that meta-analysis because of the difference in aprepitant dosing. This study does not meet the predefined requirement for homogeneity (pg 20).	Agree. Removed Navari 1999 from meta-analyses. Added clarification about difference in formulation and dosage used in this trial.
1	Results	Further discussion of Herrington, though irrelevant to this	Removed Herrington 2008 from

		question: Similarly, the reported findings of the Herrington paper suggest potential biases. This *pilot* study did not stratify patients by known risk factors for chemotherapy-induced nausea and vomiting (CINV) nor were any of the differences noted statistically significant: • More patients in the three day aprepitant arm received cisplatin, an agent with high emetogenic potential. The other agents included are all moderate or low risk chemotherapeutics. As well, the combined sample size for the two aprepitant arms was 57 patients. • Two of the three arms received the same therapy on day one and yet findings during the acute period are not the same (outcomes: proportion of patients without emesis, severity of nausea using mean VAS, and percentage with no rescue medications). • The difference in outcomes during the acute phase is most likely attributed to small sample sizes and the lack of stratification for known risk factors. This pilot study did not include the comprehensive outcome of total control, which is important when considering the implications of the findings.	Key Question 1d
1	Results	These points, together, suggest that the moderate strength of evidence support for the conclusion that one day of Aprepitant is equivalent to three days is an overstatement.	The above changes resulted in tour rating of the strength of evidence to become Low
1	Results	The 2006 evidence-based guideline from ASCO on use of antiemetic for CINV (Kris, JCO 2006) cited a number of studies to justify the recommendation that patients undergoing highly emetogenic chemotherapy receive three days three days of aprepitant. Chawla, Cancer 2003 was a phase II trial to evaluate dosing for this therapy prior to FDA approval. Findings from this trial are reported on pages 102 and 111 of this report and support use of multi-day aprepitant. Two of the phase III trials examined aprepitant therapy for patients undergoing cisplatin-based therapy (Heskth, JCO 2003; Poli-Bigelli, Cancer 2003). The final trial (Warr, JCO 2005) considered treatment in women undergoing combined anthracycline and cyclophosphamide regimens for breast	Our review of the FDA's Medical Review indicated that Hesketh 2003 and Poli-Bigelli 2003 are the pivotal trials and are already included. However, we realized we had previously omitted Campos 2001 (study 012) and added this trial.

		cancer. Other studies that should be considered are the pivotal trial completed to obtain FDA approval for aprepitant, which was the basis for the dose label of three days of treatment (125 mg on day one followed by 80 mg on days two and three). However, those studies may not include different delivery methods and thus, not appropriate for inclusion in this systematic review. Nevertheless, these are critical trials to consider if recommendations about dosing regimens for aprepitant are proposed.	
1	Discussions/Conclusions	Additional Trials for Consideration o Radiation-Induced Nausea and Vomiting (RINV): One relevant study is from Wong 2006, which was an intergroup study. All patients received ondansetron and were randomized to treatment with dexamethasone or placebo.	We excluded Wong 2006 because it compared dual therapy to monotherapy with a 5-HT3 antagonist alone, and therefore does not meet the inclusion criteria.
1	Discussions/Conclusions	Conclusions outside the scope of this systematic review o The methodology crafted by the CMS team in cooperation with the report authors was designed to answer questions about route of delivery, comparing oral and intravenous delivery of antiemetic therapies. Relevant trials were excluded because drugs approved outside the U.S. were included, specifically tropisetron. o For example, the Abali paper published in Cancer Investigation, 2007 compared ondansetron, granisetron, and tropisetron. This study could have been included without assessment of the tropisetron study but was deemed outside the scope.	Abali 2007 was excluded because all drugs were given by intravenous delivery, and therefore does not meet the inclusion criteria.
1	Discussions/Conclusions	The narrow request from CMS limited the authors' ability to consider the broader antiemetic literature. This review does not reflect the entire body of antiemetic literature evaluating therapies for patients undergoing moderate and high risk chemotherapy. As such, commentary beyond the differences and similarities between oral and intravenous delivery methods is without sufficient evidentiary basis. Assessment of such questions requires completion of a systematic review with a broader set of inclusion and exclusion criteria.	Agree

3	Discussions/Conclusions	The Summary and Conclusions section is concise and summarizes the data well. Tables 8, 9 and 10 are much longer than the narrative. This reviewer is mildly bothered by the presence of these tables here, rather than in the sections above specifically related to the key questions.	Moved tables to ends of related sections.
1	Tables	Headers for tables should be include across all pages, including evidence tables and Appendix D	Agree. Added headers where applicable.
2	Tables	Table formatting in some cases diminishes readability. 1. Results are not presented in a consistent manner, diminishing the ability to easily compare data from tables between trials. 2. Organization of studies within tables is not immediately clear; alphabetizing would assist readers. 3. Doses for all therapies should be included, whether it was part of the study regimen or control. Particularly important for dexamethasone, where different doses are indicated when aprepitant is used versus when only used with a 5HT3 antagonist. 4. Include sample sizes in each treatment group on the results tables as well as an abbreviated description of the treatment arm (see pages 108, Warr and 112, Hesketh)	Thank you. We always welcome suggestions for ways to improve the readability of our Evidence Tables and have made the suggested changes.
3	Tables	Table 1 is good. No suggested changes. Table 2 is clear and important to readers not familiar with these reviews. No suggested changes. Table 3 is well done and clear. No suggested changes. Table 4: No suggested changes Table 5: No suggested changes Table 6: No suggested changes Table 7: No suggested changes	Noted
3	Tables	Table 8: One formatting change is suggested. The subquestions 1.A., 1.C., and 1.D., all get a separate subheading with the outcomes each getting a line below. Even though subquestion 1.B. did not have any studies and thus no data, you might split this into 2 lines, so that formatting is consistent throughout the table. The content is fine.	Formatting change made.
3	Tables	Table 9: If you accept the formatting suggestion made for	Formatting change made.

		Table 8, carry this into Table 9 as well. Given the paucity of information addressing key question 2, I found the formatting in Table 9 less objectionable than when I noted it in Table 8. The content is fine.	
3	Tables	Table 10: No suggested changes.	Noted
3	Figures	Figure 1 is very clear and important. No suggested changes. Figures 2, 3 are clear and show the data from the studies in an easily understood fashion.	Thank you
1	Appendices	Please see previously stated comments.	Noted
3	Appendices	Appendix A: The glossary is a welcome addition to a work such as this and appears to be complete. Appendix B: Important to include but not interesting to most readers. Those skilled at literature searches will be able to discern whether any strategies were flawed. To my eye, the search strategies seemed appropriate. Appendix C: This methods appendix is important and clearly shows how the reviewers categorized the studies reviewed. Appendix D: No suggested changes. Appendices E, F & G: The three appendices that explain the strength of evidence of the various studies used to address the key questions are extremely important. They are clear and no changes are suggested.	Noted
3	References	The 48 references cited are appropriate and span the timeframe of these modern medicine (‘90s and ‘00s).	Noted

[1] Peer reviewers are not listed in alphabetical order.

[2] If listed, page number, line number, or section refers to the draft report.

[3] If listed, page number, line number, or section refers to the final report.