

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Oral Mechanical Bowel Preparation for Colorectal Surgery

#### I. Background and Objectives for the Systematic Review

##### Nature and Burden of the Condition

Oral mechanical bowel preparation (OMBP) is often prescribed preoperatively for patients having elective colorectal surgery in the United States.<sup>1</sup> Colorectal surgery is a frequent procedure; in 2009, there were 254,000 surgeries categorized as partial excisions of the large intestine.<sup>2</sup> Of these, 99.2 percent were for patients 15 years of age or older, and 50.4 percent were for patients 65 years of age or older. An analysis of claims from one large insurer demonstrated that the most common indication for colorectal surgery was cancer (43.9%), followed by diverticulitis (30.4%) and inflammatory bowel disease (4.5%).<sup>3</sup> As a precautionary measure, in case of possible bowel perforation, OMBP is sometimes prescribed for other abdominal and pelvic surgeries, typically urologic or gynecologic procedures, even if they are not intended to involve the colon or rectum. OMBP is also routinely prescribed prior to colonoscopy (screening, diagnostic, and therapeutic) to allow maximal visualization of the intraluminal bowel during the procedure.<sup>4</sup>

OMBP has been considered necessary to prevent infectious complications, mainly based on the belief that postoperative morbidity is related to spillage of septic bowel contents during surgery and anastomotic leakage immediately after surgery, resulting in infections.<sup>5</sup> Gross spillage of fecal material in the operative field typically induces most surgeons to create an ostomy, which impacts patients' quality of life. An ostomy, in turn, results in additional surgeries to reverse it and possibly other surgeries for complications such as bowel obstructions, incisional hernia repairs, and readmissions due to complications from these surgeries.<sup>6,7</sup> Complication rates for elective colorectal surgery range between 4 and 36 percent.<sup>8,9</sup> A surgical site infection can increase the hospitalization stay from around 4 days to around 21 days and increase costs from roughly \$11,000 to \$43,000.<sup>8</sup> A recent study of more than 10,000 patients who had undergone colorectal surgery reported that the 90-day readmission rate was 23.3 percent and the surgical site infection rate was 18.8 percent within 30 days according to data collected from a commercial insurance database.<sup>3</sup> The median cost for a surgical site infection readmission was \$12,835. The large potential cost of infections and readmissions makes this a policy issue, as coverage of preventable readmissions might be denied by some insurers in the future.

OMBP is commonly used in the United States preoperatively for elective colorectal surgery. A 2003 survey in the United States showed that more than 99 percent of colorectal surgeons routinely employed OMBP.<sup>10</sup> A recent study (2007–2009) of 24 Michigan hospitals reported that 86 percent of all colorectal surgeries were preceded by OMBP (49.6% without oral antibiotics and 36.4% with oral antibiotics).<sup>11</sup> In addition, anecdotal data from a recent meeting of the American Society of Colon and Rectal Surgeons (audience response; information provided by the topic nominator) indicated that OMBP use is still widespread in the United States. Some surgeons have discontinued use of OMBP for right-side colon surgery, but not for left-side colon and rectal surgery, apparently in response to international trials and meta-analyses.

The use of OMBP prior to colorectal surgery originally was not based on high-quality evidence but rather on expert opinion and observational data.<sup>12,13</sup> Recently, several trials (mostly conducted in Europe) have not identified a statistically significant benefit for OMBP with colon surgery (for a systematic review see Guenaga et al.<sup>1</sup>); for this reason, the practice has largely been discontinued in Europe. The 2010 guidelines of the Canadian Society of Colon and Rectal Surgeons state that good evidence supports the omission of OMBP in the preoperative management of patients undergoing elective right-sided and left-sided colorectal surgical resections.<sup>14</sup> However, the guidelines also state that the evidence for patients undergoing low anterior resection (with or without diverting stomas) is insufficient to support or refute the omission of OMBP. In Australia, OMBP is not used, and some surgeons intentionally constipate patients to facilitate removal of solid feces during surgery. International comparisons of OMBP practice patterns and their impact on infections and leaks are confounded by other differences in perioperative care across countries. For example, in England, where OMBP is no longer recommended,<sup>15</sup> surgeons use early postoperative feeding.

### **Clinical Use of OMBP**

OMBP is usually started by the patient at home the day before surgery or colonoscopy. Elderly and frail patients may undergo OMBP in the hospital. An enema is sometimes given the night before or morning of surgery. The commonly used OMBP agents are preparations approved by the U.S. Food and Drug Administration that are available over the counter in the United States. Oral polyethylene glycol (PEG) solutions evacuate the bowel by washout of ingested fluid (four liters), with no substantial fluid or electrolyte shifts.<sup>8</sup> Bisacodyl, a poorly absorbed diphenylmethane, stimulates colonic peristalsis and requires a lesser volume of ingested fluid (2 liters).<sup>4</sup> The most commonly used oral laxative agents currently are over-the-counter, large-volume, osmotically balanced PEG solutions (e.g., MiraLAX®, GoLYTELY®, NuLYTELY®) or reduced-volume PEG with the addition of bisacodyl (HalfLytely®). Hyperosmotic sodium phosphate preparations draw water into the bowel to achieve washout.<sup>4</sup> Previously, sodium phosphate hyperosmotic preparations (Fleet®) were used, but this has been largely discontinued because of concern about electrolyte imbalance.

Patients dislike the large quantities of unpleasant-tasting laxative solutions required and the long hours on the toilet. A minority of patients requires medical attention for vomiting, dehydration, and other reactions to OMBP; this may require cancellation and rescheduling of surgery. Additionally, liquid bowel contents from OMBP use may be less safely handled during surgery than solid contents. This is proposed as an explanation for why some studies have reported greater infection rates with OMBP than without it. Individuals who may be at greater risk of adverse effects of OMBP are the elderly ( $\geq 65$  years of age) and those with comorbidities such as cardiovascular and pulmonary disease, diabetes, kidney disease, and compromised immune conditions.

**Use of OMBP in patients undergoing colonoscopy:** OMBP is also used to prepare patients for diagnostic colonoscopy. Because adverse events are commonly not well reported in surgical trials, including studies of OMBP for diagnostic colonoscopy could provide additional data for some of the adverse events caused by OMBP, particularly for patient subgroups. However, data collected in the colonoscopy setting may not be directly transferable to surgical settings: it is likely that the surgical procedure itself interacts with the OMBP to affect at least some of the adverse events that are observed. For example, surgical patients can have a complex postsurgical

course to which OMBP may contribute (e.g., favorably by reducing complications from leakage or unfavorably by inducing fluid or electrolyte imbalance). In addition, the bowel integrity is maintained in typical (uncomplicated) colonoscopic procedures but not in surgical procedures. Further, modifiers of relative adverse events are likely to be substantially different between the surgical and colonoscopic settings. Finally, data on adverse events from the colonoscopy population may not be applicable to surgical populations, if the two differ in important patient characteristics. For these reasons, and following discussions with the Technical Expert Panel (TEP) convened for this review, we decided that the current review will be limited to patient populations undergoing elective colorectal surgery.

## Antibiotics

Oral and/or intravenous antibiotics may also be given perioperatively. Mechanical cleansing of the large intestine decreases the total volume of stool in the colon but does not change the concentration of bacteria.<sup>16</sup> For this reason, in addition to the intravenous antibiotics routinely given immediately before and during surgery, some surgeons also prescribe oral antibiotics before colon surgery. A common oral antibiotic regimen is the Nichols-Condon bowel prep and consists of neomycin and erythromycin given the day before surgery.<sup>17</sup> Metronidazole (500 mg) has been substituted for the erythromycin because of its increased effectiveness against anaerobic organisms in the gut. Differences in antibiotic regimens between trials may complicate comparisons of postoperative infection rates among trials and may be a source of heterogeneity in meta-analyses. Decreased infection rates have been reported when oral antibiotics are added to intravenous antibiotics and OMBP.<sup>11,18</sup> Bellows et al.<sup>18</sup> have suggested that oral antibiotics are most effective after the burden of colonic bacteria has been reduced by means of OMBP. If surgeons in the United States start performing colorectal surgery without OMBP, this raises the formal question of the effect of oral antibiotics without OMBP.

## Uncertainty and the Rationale for an Evidence Review

A recent systematic review by the Cochrane Collaboration (covering studies up to December 1, 2010), did not identify a statistically significant benefit in favor of OMBP in terms of anastomotic leaks, other surgical complications, or mortality for mixed populations of patients undergoing colon or rectal resection.<sup>1</sup> Despite these results, large variation in practice exists in different parts of the world, perhaps suggesting that published reviews do not adequately address all decisionmaking uncertainties. Further, our own preliminary searches have identified additional studies that are likely to be included in an updated review. Specifically, two studies—Sasaki et al.<sup>19</sup> and Bertani et al.<sup>20</sup>—have been published and appear relevant to the comparisons of interest. These studies are fairly large and thus have the potential to influence the analyses substantially. In addition, they include patients undergoing laparoscopic resection, a subset of patients that the Cochrane review identified as under-represented in the corpus it covered.<sup>1</sup> In addition, a single study included in the Cochrane review has recently been retracted<sup>21,22,a</sup> and should probably be removed or subjected to sensitivity analysis. This is potentially important because this study represented the second or third largest available study in many of the

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<sup>a</sup> The retraction notice stated that “large portions of text [...] have been duplicated from another article previously published in *Annals of Surgery*.” In fact, the text of the two publications is identical (despite being conducted by different research teams based in different countries), raising concerns about the truthfulness of reporting in the second study. We argue that the retracted study should not be included at all in a meta-analysis.

comparisons examined by the Cochrane review. Perhaps more importantly, available reviews do not provide information that is directly usable to decisionmakers. Specifically, current reviews do not adequately examine the comparative effectiveness of all feasible alternative bowel-preparation strategies. Existing reviews have relied on pairwise comparisons between interventions, often lumping different OMBP methods or combining control groups who receive no intervention with groups using enemas. This approach may introduce heterogeneity (if alternative OMBP methods have different effectiveness or if enemas are superior to no intervention) and is not helpful in identifying the “best” OMBP approach. By contrast, a joint synthesis of data on all relevant treatment options using network meta-analysis (e.g., OMBP based on liquid volume only; OMBP using drugs that cause increased peristalsis; the previous two combined with enema; enema alone; only antibiotics and no OMBP or enema) can provide information on which treatment is likely best.

Given the uncertainty about the impact of OMBP (particularly with regard to subgroups as defined by location of the surgery), the need to update existing reviews to reflect recent changes in the published evidence and the potential to synthesize the evidence using more informative analytical approaches, a systematic review of the available evidence on the benefits and adverse events of importance to stakeholders will help inform medical decisions about the use of OMBP. This updated review would also address potential modifiers of the OMBP effect on outcomes, including procedural or patient characteristics (e.g., location of the surgery [right colon vs. left colon vs. rectum], use of oral antibiotics, surgical technique [laparoscopic vs. open], patient age or comorbidities, etc.).

## II. The Key Questions

On the basis of input from clinical experts during Topic Refinement, we have developed the following Key Questions (KQs) and study eligibility criteria to clarify the focus of the proposed systematic review. The following two KQs will be addressed in the review:

<b>KQ 1:</b>	<p>How do various preoperative OMBP strategies compare between them and versus a control with respect to their effectiveness for preventing surgical or postsurgical complications?</p> <ol style="list-style-type: none"> <li>a. For elective <i>right colon</i> surgery?</li> <li>b. For elective <i>left colon</i> surgery?</li> <li>c. For elective <i>rectal</i> surgery?</li> </ol>
<b>KQ 2:</b>	<p>How does the use of OMBP, with or without cointerventions (e.g., antibiotics, rectal enema), compare with no OMBP or with OMBP plus different cointerventions with respect to presurgical and postsurgical adverse events?</p> <ol style="list-style-type: none"> <li>a. What are the comparative adverse events of the various OMBP strategies?</li> <li>b. What are the comparative adverse events of OMBP in subgroups of patients especially susceptible to the potential adverse events?</li> </ol>

### Populations

- KQ 1: Adults and children who undergo elective colon (KQ 1a and 1b) or rectal surgery (KQ 1c); additional subgroups of interest will be those defined by anastomosis location and type, type of surgical procedure (open vs. laparoscopic), patient age (children vs.

adults), and indications for surgery (cancer vs. inflammatory bowel disease vs. diverticulitis vs. other)

- KQ 2a (adverse events): Adults and children who undergo elective colon or rectal surgery
- KQ 2b (adverse events, susceptible subgroups): Adults and children with cardiovascular or pulmonary disease, extremes of age (young children and the elderly), patients who have undergone adjuvant chemotherapy or radiotherapy, and patients with diabetes, kidney disease, or compromised immune function (including drug-induced immunosuppression) who undergo elective colorectal surgery
- The following populations will not be considered within the scope of the review: Patients receiving OMBP in preparation for endoscopic procedures; patients who present with complete bowel obstruction requiring surgical or endoscopic intervention to initiate OMBP

### **Interventions**

- All KQs: OMBP before colon or rectal surgery
- Cointerventions: Oral antibiotics given before colon and rectal surgery, such as neomycin, erythromycin, and metronidazole; rectal enema
- The following interventions will not be considered within the scope of the review: Mechanical bowel preparation not through the oral route (e.g., retrograde preparation)

### **Comparators (for all Key Questions)**

- Alternative preparation strategies, with or without antibiotics or enema
- No OMBP

### **Outcomes**

- Intermediate outcomes
  - Clinical outcomes
    - a. Infectious outcomes (classified according to the definitions proposed by the Centers for Disease Control and Prevention; available at [www.cdc.gov/hicpac/SSI/002\\_SSI.html#IB1](http://www.cdc.gov/hicpac/SSI/002_SSI.html#IB1); last accessed February 11, 2013)
    - b. Anastomotic leakage
    - c. (Unplanned) ostomies; failed attempts to restore bowel continuity
    - d. Venous thromboembolism (deep venous thrombosis and pulmonary embolism)
  - Health system outcomes and resource utilization
    - a. Readmissions after surgery
    - b. Reoperation
    - c. Additional interventional procedures (endoscopy, interventional radiology)
    - d. Length of stay (postoperative and overall)
    - e. Admission to intensive care unit
    - f. Admission to nursing care
  - Patient-centered outcomes
    - a. Patient satisfaction
    - b. Quality of life
- Terminal clinical outcome

- Mortality
- Adverse events
  - Nausea
  - Vomiting
  - Dehydration
  - Electrolyte imbalance
  - Kidney damage
  - Emergency admissions prior to surgery
  - Cancelled, delayed, or rescheduled surgeries
  - Allergic reactions
  - Seizures

### **Timing**

- Studies will not be excluded on the basis of followup duration.
- When possible, outcome data (for beneficial and adverse events) will be evaluated separately for the preoperative and postoperative periods.

### **Setting**

- No restrictions

### III. Analytic Framework

Figure 1 presents a schematic of the analytic framework for this report.

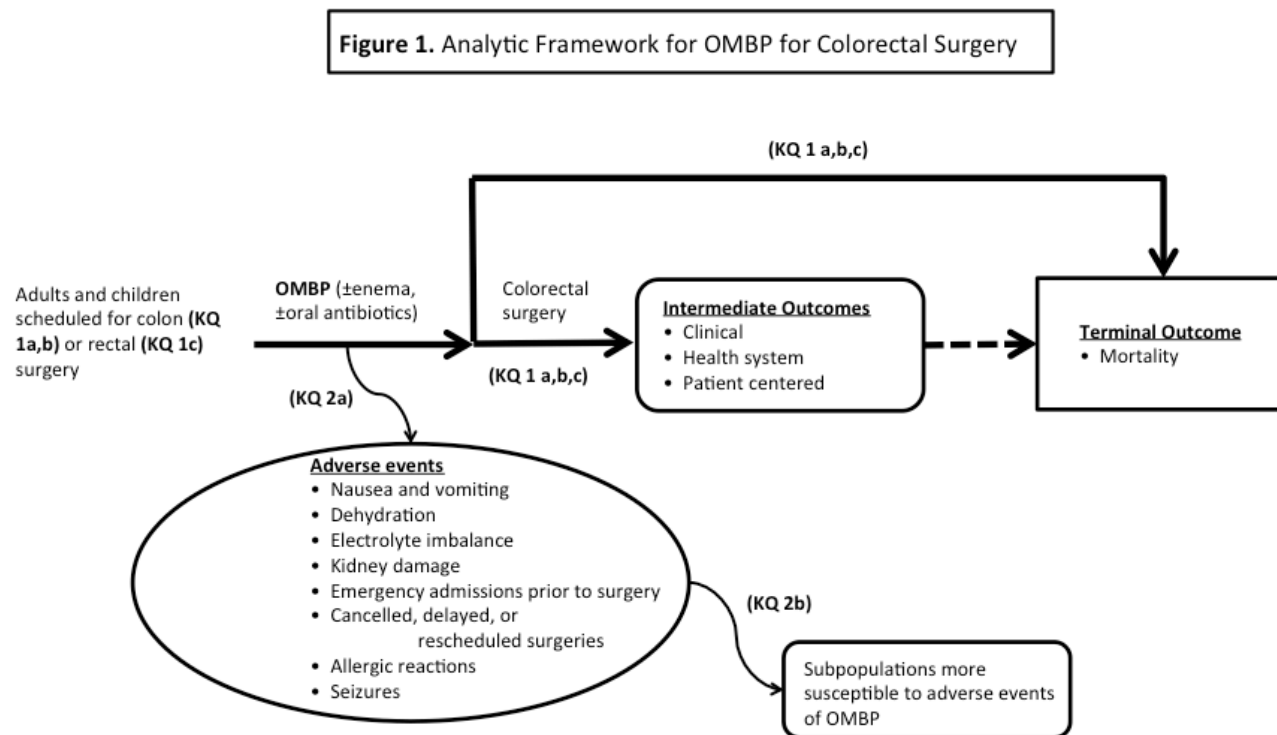


Figure 1. Key Questions are shown within the context of the PICO (population, intervention, comparators, and outcomes) criteria. Interventions (alternative OMBP strategies or no OMBP) are compared in relevant clinical populations (patients undergoing elective large bowel surgery) with regard to intermediate outcomes (e.g., anastomotic leakage, reoperation, costs, etc.), final outcomes (mortality), or adverse events (e.g., nausea, vomiting, etc.). The treatment effect may be modified by several patient-level factors (e.g., cointerventions, location of the surgery, use of antibiotics, etc.). Please see the preceding section for a detailed description of the populations, interventions, and outcomes of interest. Abbreviations: KQ = key question; OMBP = oral mechanical bowel preparation.

## IV. Methods

### A. Additional Criteria for Inclusion/Exclusion of Studies in the Review

We will use the eligibility criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs and setting (PICOTS) as described for the KQs (Section II above). Here, we provide some additional details about the inclusion and exclusion criteria we plan to use for each KQ. These criteria were chosen on the basis of a preliminary review of the literature, general principles of study design, and extensive discussions with TEP members.

#### Key Questions 1a and 1b

- Randomized parallel-arm studies comparing at least two of the interventions of interest in patient populations undergoing elective colon or rectal surgery

We will require that studies have enrolled at least 10 subjects (per arm); smaller sample sizes are unlikely to provide estimates of treatment effects that are adequately precise.

- Nonrandomized comparative studies (prospective or retrospective; observational or experimental) comparing at least two of the interventions of interest in patient populations undergoing elective colon or rectal surgery

We will require that studies have enrolled at least 100 subjects (per arm); this cutoff was chosen to allow for the use of statistical methods to control for confounding.<sup>a</sup>

#### Key Question 2a (Adverse Events):

- Randomized parallel-arm studies comparing at least two of the interventions of interest in patient populations undergoing elective colon or rectal surgery

We will require that studies have enrolled at least 10 subjects (per arm); smaller sample sizes are unlikely to provide estimates of treatment effects that are adequately precise.

- Nonrandomized comparative studies (prospective or retrospective; observational or experimental) comparing at least two of the interventions of interest in patient populations undergoing elective colon or rectal surgery

We will require that studies have enrolled at least 100 subjects (per arm).

- Single-group studies (i.e., cohort studies where all patients are managed with

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<sup>a</sup> Assuming that at least three potential confounders are to be considered, regression models have to include at least four predictor variables (one per confounder and the treatment indicator). Using the (fairly liberal) “rule of 10,” this means that a study needs to include at least 40 ( $= 4 \times 10$ ) outcome events for statistical analysis. Even if the outcome rate is 10 percent (i.e., quite high), the sample size needs to be  $>400$  patients.



OMBP or alternative strategies) and then undergo elective colon or rectal surgery. We will only include single-group studies if they have enrolled at least 200 individuals. This cutoff is chosen to ensure that studies can estimate low event rates with adequate precision.<sup>b</sup>

### **Key Question 2b (Adverse Events, Susceptible Subgroups)**

- The same as for KQ 2a, with the additional requirement that studies report formal interaction tests or allow for the calculation of statistics that compare the treatment effect among strata of the modifier of interest

### **Additional Criteria**

- For all KQs, we will exclude primary research studies reporting results on the use of OMBP on patients not undergoing colorectal surgery or on mixed populations in which less than 80 percent of patients underwent colorectal surgery (unless data on the subgroup undergoing colorectal surgery are reported separately).
- For all KQs, we will exclude primary research studies in emergency settings, including studies where interventional methods (e.g., colonoscopic stenting) are used to relieve bowel obstruction before OMBP.
- For all KQs, we will exclude primary research studies on animals, as well as editorials, commentaries, narrative reviews, letters to the editor, and other manuscripts not reporting primary research findings.

## **B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions**

Appendix 1 describes our proposed literature search strategy. This search will be conducted in MEDLINE<sup>®</sup>, EMBASE<sup>®</sup>, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL<sup>®</sup>) database. These databases were chosen after a preliminary review of existing systematic reviews on OMBP and discussions with the TEP. We will not restrict searches by year of publication. We will also perform a search for systematic reviews on the topic and use their reference lists of included studies to validate our search strategy and to make sure we can identify all relevant studies.

A common set of 400 abstracts (in 2 pilot rounds, each with 100 abstracts) will be screened by all reviewers, and discrepancies will be discussed in order to standardize screening practices and ensure understanding of screening criteria by all team members. The remaining citations will be split into nonoverlapping sets, each screened by two reviewers independently. Discrepancies will be resolved by consensus involving a third investigator.

Potentially eligible citations (i.e., abstracts considered potentially relevant by at least one reviewer) will be obtained in full text and reviewed for eligibility on the basis of the predefined inclusion criteria. Full-text articles will be screened independently by two reviewers for eligibility. Disagreements regarding article eligibility will be resolved by consensus involving a third reviewer. We plan to include only English-language studies during the full-text review because our preliminary searches indicate that non-English-language studies are few and have small sample sizes; as such, they are unlikely to affect our conclusions. We may reconsider this

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<sup>b</sup>For example, assuming the true incidence proportion is 0.01 (=1%) the probability of observing at least one event is >85 percent for a study of 200 patients.

decision if large relevant studies are identified during full-text screening. To accommodate this potential modification of our inclusion criteria, we will not use language of publication as a criterion at the abstract screening stage (instead, we will evaluate the language of publication only at the full-text review stage). We will exclude studies published exclusively in abstract form (e.g., conference proceedings) because they are typically not peer reviewed, only partially report results, and may change substantially when fully published. We will generate a list of reasons for exclusion for all studies excluded at the full-text screening stage.

We will ask the TEP to provide citations of potentially relevant articles. Additional studies will be identified through the perusal of reference lists of eligible studies, published clinical practice guidelines, relevant narrative and systematic reviews, conference proceedings, Scientific Information Packages from manufacturers, and a search of U.S. Food and Drug Administration databases. All articles identified through these sources will be screened for eligibility against the same criteria as for articles identified through literature searches. If necessary, we will revise the search strategy so that it can better identify articles similar to those missed by our current search strategy. We will also ask the TEP to review the final list of included studies to ensure that no key publications have been missed.

Following submission of the draft report, an updated literature search (using the same search strategy) will be conducted. Abstract and full-text screening will be performed as described above. Any additional studies that meet the eligibility criteria will be added to the final report.

### **C. Data Abstraction and Data Management**

Data will be extracted into standard forms. The basic elements and design of these forms will be the similar to those we have used for other effectiveness reviews and will include elements that address population characteristics, sample size, study design, descriptions of the interventions and comparators of interest, analytic details, and outcome data. Prior to extraction, forms will be customized to capture all elements relevant to the KQs. We will use separate sections in the extraction forms for KQs related to intermediate outcomes, terminal outcomes, or adverse events and for factors affecting (modifying) the treatment effect among subgroups of patients. We will pilot test the forms on several studies extracted by all team members to ensure consistency in operational definitions. If necessary, forms will be revised before full data extraction. We will also consult with the TEP to ensure that all items of clinical or research importance are captured; the final extraction form will be circulated to the TEP members for review.

Data from each eligible study will be extracted by a single reviewer. The extracted data will be reviewed and confirmed by at least one more team member (data verification). Disagreements will be resolved by consensus including a third reviewer.

We will contact authors (1) to clarify information reported in the papers that is hard to interpret (e.g., inconsistencies between tables and text); (2) to obtain missing data on key subgroups of interest when not available in the published reports (e.g., location of the surgery—right or left colon, rectum); and (3) to verify suspected overlap between study populations in publications from the same group of investigators. Author contact will be by email (to the corresponding author of each study), with a primary contact attempt (once all eligible studies have been identified) and up to two reminder emails (approximately 2 and 4 weeks after the first attempt).

### **D. Assessment of Methodological Risk of Bias of Individual Studies**

We will assess the risk of bias for each individual study using the assessment instrument detailed by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Review* hereafter referred to as the *Methods Guide*. For randomized comparative studies, we will base our assessment on items from the Cochrane risk of bias tool for randomized controlled trials.<sup>23</sup> For nonrandomized comparative studies and single-group studies, we will use items from the Newcastle-Ottawa tool,<sup>24</sup> with the addition of items relevant to statistical analysis.<sup>25</sup>

We will not merge items into “composite” quality scores. Instead, we will assess and report each methodological quality item (as Yes, No, or Unclear/Not Reported) for each eligible study. We will rate each study as being of low, intermediate, or high risk of bias on the basis of adherence to accepted methodological principles. Generally, studies with low risk of bias have the following features: lowest likelihood of confounding due to comparison to a randomized controlled group; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; clear reporting of dropouts and a dropout rate less than 20 percent; and no apparent bias. Studies with moderate risk of bias are susceptible to some bias but not sufficiently to invalidate results. They do not meet all the criteria for low risk of bias owing to some deficiencies, but none are likely to introduce major bias. Studies with moderate risk of bias may not be randomized or may be missing information, making it difficult to assess limitations and potential problems. Studies with high risk of bias are those with indications of bias that may invalidate the reported findings (e.g., observational studies not adjusting for any confounders, studies using historical controls, or studies with very high dropout rates). These studies have serious errors in design, analysis, or reporting and contain discrepancies in reporting or have large amounts of missing information.

In quantitative analyses, we will consider performing subgroup analyses to assess the impact of each quality item on the meta-analytic results. The grading will be outcome specific, such that a given study that reports its primary outcome well but did an incomplete analysis of a secondary outcome would be graded of different quality for the two outcomes. Studies of different designs will be graded within the context of their study design. Thus, randomized controlled trials will be graded as having a high, medium, or low risk of bias, and observational studies will be separately graded as having a high, medium, or low risk of bias.

## **E. Data Synthesis**

We will summarize included studies qualitatively and present important features of the study populations, designs, interventions, outcomes, and results in summary tables. Population characteristics of interest include age, sex, indication for OMBP, and patient comorbidities. Design characteristics include methods of population selection and sampling and followup duration. Intervention characteristics include the specific OMBP method used and the coadministration of oral antibiotics. We will consider (a) intermediate outcomes (readmissions after surgery, reoperation, costs, patient satisfaction, quality of life), (b) terminal outcomes (mortality), and (c) adverse effects of interventions (nausea, vomiting, dehydration, electrolyte imbalance, kidney damage, emergency admissions prior to surgery; cancelled, delayed, or rescheduled surgeries).

For each comparison of interest, we will judge whether the eligible studies are sufficiently similar to be combined in a meta-analysis on the basis of clinical heterogeneity of patient populations and interventions and testing strategies, as well as methodological heterogeneity of

study designs and outcomes reported. Single group studies of OMBP will be synthesized (qualitatively and, if appropriate, quantitatively) to better evaluate (and if statistical analyses are deemed appropriate, to estimate more precisely) the adverse event rate among patients receiving the interventions of interest. Study-level or summary estimates of event rates will also be used to contextualize the relative effects observed in comparative studies. We do not plan to statistically combine single-group and comparative studies.

On the basis of discussions with the TEP and our own review of several trials of OMBP we expect that eligible studies will have employed a variety of interventions (e.g., different substances are used for preparation, with or without enema, and with or without antibiotics) and assessed heterogeneous outcomes. Furthermore, we expect that the completeness of outcome definitions may be suboptimal. To address these issues we have decided to seek input from TEP members to define groups of “sufficiently similar” interventions and outcomes for synthesis (including meta-analysis) during later stages of the review. TEP members’ input will be solicited by providing a list of interventions (including data on specific preparation regimens, doses, duration of preparation, and co-interventions) and a list of outcomes (along with outcome definitions, when available) from the eligible studies. Of note, the material used to solicit input will not include any data on outcome results extracted from the studies (to limit the potential for bias).

The determination on the appropriateness of meta-analysis will be made *before* any data analysis; we will not base the decision to perform meta-analysis on statistical criteria for heterogeneity. Such criteria are often inadequate (e.g., low power when the number of studies is small) and do not account for the ability to explore and explain heterogeneity by examining study-level characteristics. Main analyses will include all relevant studies (e.g. studies of colon and rectum surgeries, and those with mixed populations); subgroup analyses (e.g., separately by anatomic site of surgery, or by year when study enrollment was started) will also be performed. The concordance of findings across subgroup analyses will be evaluated qualitatively (in all instances) and quantitatively (using meta-regression, when the data allow). In cases when only a subset of the available studies can be quantitatively combined (e.g., when some studies are judged to be so clinically different from others as to be excluded from meta-analysis) we will synthesize findings across all studies qualitatively by taking into account the magnitude and direction of effects.

We expect that studies will have compared different interventions (e.g. OMBP based on liquid volume only; OMBP using drugs that cause increased peristalsis; the previous two combined with enema; enema alone; no OMBP or enema – only antibiotics). For this reason we anticipate using methods that combine direct and indirect evidence (network meta-analysis and mixed treatment comparisons).<sup>26-28</sup> Regardless of whether such analyses will be possible in the final set of included studies, we expect to perform direct pairwise meta-analyses comparing pairs of interventions at least for the following two comparisons (as reported in the 2011 Cochrane review on the same topic<sup>1</sup>): OMBP vs. no preparation and OMBP vs. rectal enema.

#### Pairwise meta-analyses

Direct pairwise meta-analyses will be undertaken when there are more than three unique studies evaluating the same intervention and comparator and reporting the same outcomes. All meta-analyses will be based on random effects models.<sup>29</sup> Sensitivity analyses (including leave-one-out analyses, analyses assuming a fixed effects model, and reanalyses after excluding a group of studies) may be undertaken if considered appropriate (e.g., in the presence of studies with outlying effect sizes or evidence of temporal changes in effect sizes). For all statistical tests,

except those for heterogeneity, statistical significance will be defined as two-sided  $P < 0.05$ . Heterogeneity will be considered statistically significant when the  $p$ -value of the  $Q$  statistic is  $P < 0.1$ , to account for the low statistical power of the test.<sup>30</sup> We will attempt to explore between-study heterogeneity using subgroup and meta-regression analyses; the decision to quantitatively synthesize studies will not be based on statistical tests for heterogeneity.<sup>31</sup>

#### Network meta-analysis

The grouping of alternative interventions into categories will be decided on the basis of the information provided in the published studies and input from our TEP (see below); as such we cannot provide details about the network structure (e.g. number of nodes) at this time. Based on the final grouping we will examine the network architecture and specify the analytic model. In general, we expect that we will use a generalized linear model with an appropriate variance structure (e.g., binomial for binary outcomes; normal for continuous outcomes) and link function (e.g., logit for binomial outcomes; identity for continuous outcomes) for each outcome of interest.<sup>34</sup> Models will account for between-study heterogeneity for each comparison of interest; if the data are sufficient, we will also evaluate the consistency of direct and indirect effects using established methods. All models will be fit using Bayesian methods because they offer additional modeling flexibility (when compared with maximum likelihood approaches) and because they allow direct probabilistic statements to be made regarding the magnitude and direction of the treatment effect.

We will obtain estimates of the treatment effects of interest (e.g., odds ratios for anastomotic leakage comparing different types of OMBP vs. no OMBP), as well as the rank probabilities for each treatment strategy (e.g., probability that a type of OMBP is the “best treatment”). We will also report probabilities that the difference (in the odds ratio scale) between pairs of treatments is larger than 1, 1.10, 1.25, 1.5, 2.0, 3.0, and 5.0. These cutoffs were chosen after discussion with the TEP.

### **F. Grading the Strength of Evidence for Individual Outcomes**

We will follow the *Methods Guide*<sup>35</sup> to evaluate the strength of the body of evidence for each KQ with respect to the following domains: risk of bias, consistency, directness, precision, and reporting bias.<sup>35</sup>

Briefly, we will define the *risk of bias* (low, medium, or high) on the basis of the study design and the methodological quality of the studies. We will rate the *consistency* of the data as no inconsistency, inconsistency present, or not applicable (if there is only one study available). We do not plan to use rigid counts of studies as standards of evaluation (e.g., four of five studies agree, therefore the data are consistent); instead, we will assess the direction, magnitude, and statistical significance of all studies and make a determination. We will describe our logic where studies are not unanimous. We will assess *directness* of the evidence (“direct” vs. “indirect”) on the basis of the use of surrogate outcomes or the need for indirect comparisons (e.g., when treatments have not been directly compared and inference is based on observations across studies). We will assess the *precision* of the evidence as precise or imprecise on the basis of the degree of certainty surrounding each effect estimate. A precise estimate is one that allows for a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions and that therefore precludes a conclusion.

The potential for *reporting bias* (“suspected” vs. “not suspected”) will be evaluated with respect to publication bias, selective outcome reporting bias, and selective analysis reporting bias. For reporting bias, we will make qualitative dispositions rather than perform formal

statistical tests to evaluate differences in the effect sizes between more precise (larger) and less precise (smaller) studies. Although these tests are often referred to as tests for publication bias; reasons other than publication bias can lead to a statistically significant result, including “true” heterogeneity between smaller and larger studies, other biases, and chance, thereby rendering the interpretation of the tests nonspecific and the tests noninformative.<sup>32,33</sup> Therefore, instead of relying on statistical tests, we will evaluate the reported results across studies qualitatively, on the basis of completeness of reporting (separately for each outcome of interest), number of enrolled patients, and numbers of observed events. Judgment on the potential for selective outcome reporting bias will be based on reporting patterns for each outcome of interest across studies. We acknowledge that both types of reporting bias are difficult to reliably detect on the basis of data available in published research studies (i.e., without access to study protocols and detailed analysis plans). Although some degree of subjectivity is unavoidable in this assessment, we will explicitly present all operational decisions and the rationale for our judgment on reporting bias in the Draft Report.

Finally, we will rate the body of evidence using four strength of evidence levels: high, moderate, low, and insufficient.<sup>35</sup> These will describe our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

### G. Assessing Applicability

We will follow the *Methods Guide*<sup>35</sup> to evaluate the applicability of included studies to patient populations of interest. We will evaluate studies (or subgroups of studies) of elderly adults (operationally defined as patients 65 years of age or older) separately if data are available. Applicability will also be judged separately for various indications of OMBP use (e.g., left-sided vs. right-sided colon surgery, rectal surgery), patient sex (men vs. women), and setting of care.

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## **VI. Definition of Terms**

Not applicable.

## **VII. Summary of Protocol Amendments**

No amendments have been made. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

## **VIII. Review of Key Questions**

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the TEP to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

## **IX. Key Informants**

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Technical Experts**

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical

or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## **XII. EPC Team Disclosures**

The following team members will be involved:

- The EPC Director
- The EPC Codirector
- One Project Lead
- One Co-Project Lead/Research Associate
- One Local Clinical Expert
- One Project Manager
- One Program Assistant

All EPC team members have no financial or other conflicts of interest to disclose.

## **XIII. Role of the Funder**

This project was funded under Contract No. HHSA-290-2012-0012-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## Appendix 1: Search Strategy

### Databases:

MEDLINE<sup>®</sup>, EMBASE<sup>®</sup>, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL<sup>®</sup>)

### Search Terms (for MEDLINE):

((surgic\* OR surgery OR surgeri\* OR operativ\* OR operation OR operations OR preoper\* OR pre-oper\* OR preoperative OR "surgery"[Subheading] OR "surgical procedures, operative"[MeSH])

AND

("colorectal"[all fields] OR colon OR coloni\* OR colore\* OR recta\* OR rectu\* OR "colorectal" OR ((large) AND (bowel\* OR intestin\*)) OR "Intestine, Large"[Mesh] OR colon[mesh] OR rectum[mesh])) OR ("Colorectal Surgery"[Mesh]))

AND

(prepara\* OR enema\* OR cathartics[MeSH] OR cathartic\* OR polyethylene glycols[MeSH] OR (polyethylene AND (glycol OR glycols)) OR phosphates[MeSH] OR phosphate\* OR "Laxatives"[MeSH] OR laxative\* OR "Senna Extract"[Mesh] OR (senna AND extract\*) OR "Bisacodyl"[Mesh] OR "bisacodyl"[all fields] OR "Cascara"[Mesh] OR "cascara"[all fields] OR "Enema"[Mesh] OR "PEG"[all fields] OR "miralax"[all fields] OR "golytely"[all fields] OR "nulytely"[all fields] OR "halflytely"[all fields] OR "fleet"[all fields] OR "dulcolax"[all fields] OR "pico salax"[all fields])

**Note:** This search will be translated for use in other databases.