School of Epidemiology and Public Health

Knowledge Synthesis Group

# *Benefits and Harms of Treatment Options for Esophageal Adenocarcinoma and Precancerous Conditions: A Protocol for an Overview of Systematic Reviews*

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# 1. Background

The Canadian Task Force for Preventive Health Care (CTFPHC) is developing a new guideline on screening for esophageal adenocarcinoma (EAC) and precancerous conditions of the esophagus, including Barrett's esophagus (BE), and dysplasia. As part of the guideline development process a series of systematic reviews (SR) is planned to address key questions focused on the effectiveness of screening for EAC, as well as patient values and preferences surrounding screening for both EAC and precancerous conditions. Narrative reviews addressing the natural history and etiology of the disease, specifically looking at the evidence linking precursors to EAC, the key risk factors for precursors and EAC, and outcomes of EAC, have also been developed. In addition to these SRs and narrative reviews, to provide the CTFPHC with a complete picture of the evidence to inform the guideline development process, an overview of SRs on the effectiveness of treatment options for early stage EAC and precancerous conditions will be performed to provide indirect evidence related to one component of the screening process. Understanding the pathway between precancerous conditions and EAC, including the effectiveness of early treatment interventions (compared to later treatment resulting from other forms of disease identification), is important to inform recommendations on screening. The use of indirect evidence is sometimes employed by the CTFPHC to inform decision making when direct evidence on the effectiveness of screening is not available (1).

There are two main types of esophageal cancer, EAC and esophageal squamous cell carcinoma (ESCC). EAC is the most common type of esophageal cancer in North America and Europe (2), and usually develops in the lower third of the esophagus, in the area where BE develops (2). ESCC can be found in any part of the esophagus, and is less common in Canada. Because of the growing incidence and high mortality rate of EAC in Canada and understanding the disease pathway of EAC in relation to existing precancerous conditions, the CTFPHC has decided the overview of SRs will focus on treatment of EAC and precancerous conditions.

Incidence rates of esophageal cancer in males have been increasing steadily since the 1970s. From 1986 to 2006 the rate of EAC doubled in men (11.8 to 3.5 per 100,000) and women (0.2 to 0.5 per 100,000), or annual increases of 3.9% in men and 3.6% in women per year. Projections of the observed trends suggest that rates of EAC will increase by an additional 40% in men (up to 4.8 per 100,000) and 50% in women (up to 0.8 per 100,000) by 2026. Five-year survival of EAC is low among both men and women, with a rate of 14% (3). This is mostly due to late stage diagnosis, where cancer has metastasized or spread to other organs. Those diagnosed early with asymptomatic EAC have better survival than those diagnosed with symptomatic disease, over 50% of whom will require palliative measures at diagnosis (4). The increase in EAC rates may be secondary to the increasing prevalence of risk factors such as obesity and gastroesophageal reflux disease (GERD) (2). Risk factors for the development of EAC are male sex, age 50 years and older, white ethnicity, chronic GERD, BMI ≥30, current or past smoking history, and a family history of BE or EAC (3,5,6,7).

The prevention of EAC via screening, early diagnosis, and treatment of precancerous conditions such as BE, and low- and high-grade dysplasia, if effective, may offer a strategy for reducing mortality and improving long term survival and quality of life of those affected.

We are not aware of any national guidelines or recommendations on treatment of EAC and precancerous conditions in Canada. Some provinces have developed guidelines, including Alberta Health Services (2014) (8) on the management of early EAC and BE which focuses on diagnosis and treatment, and the British Columbia Health Services Authority, BC Cancer division for the treatment for esophageal cancers (9). Several international organizations such as the American College of Physicians (10), the American Gastroenterological Association (11), the American College of Gastroenterology (7), the National Institute for Health and Care Excellence (12), the Society for Thoracic Surgeons (13), and the National Comprehensive Cancer Network (14) have guidelines addressing management and treatment options for EAC, BE, and low- and high-grade dysplasia.

## 1.1 Description of the condition

The most common 'alarm' symptom of EAC is dysphagia (difficulty swallowing), although many people will have no symptoms (15). Others symptoms include weight loss, bleeding, epigastric pain and persistent cough. Approximately, 20% of diagnosed cases of EAC are early EAC, limited to the mucosa or submucosa (16). Treatment with an esophagectomy at this stage leads to a five-year survival rate of 90%, but this procedure has a mortality rate of 2% and a major morbidity rate of up to 10% (16).

Although not all people with EAC experienced GERD or were diagnosed with BE, these two conditions represent risk factors for EAC, and there is some evidence (described below) of progression from GERD to BE, to low-/high-grade dysplasia, to EAC.

GERD is a condition that develops when the reflux of the stomach contents causes troublesome symptoms and/or complications (Montreal Classification) (17).. GERD is a common condition, with approximately 13% of Canadians experiencing symptoms weekly (18). It is estimated that approximately 170,000 Canadians will be newly diagnosed with GERD every year with the highest incidence among those 60-70 years of age (19). Approximately 10% of people with GERD will develop BE (8,20).

BE is the most important precancerous disease for EAC. In BE, the tissue lining the esophagus changes to intestinal metaplasia (resembling the tissue lining of the intestines). It is unknown how these changes occur, but it has been proposed that the acid regurgitation associated with GERD may prompt changes at the cellular level (21).In Canada, studies have estimated the prevalence of BE among primary care patients at 2.4% (22). The prevalence of BE is between 1-2% among those who undergo an esophagogastroduodenoscopy (EGD) (also called upper GI endoscopy) for any reason, and between 5-15% among those who receive an EGD for symptoms of GERD (23). Most people with non-dysplastic BE or only low-grade dysplasia (cellular change), will not develop cancer. However, some reports indicate those with a diagnosis of BE carry a 30- to 125-fold higher risk of developing EAC than those in the general population (whether dysplasia was present was not indicated) (24).. The annual incidence of EAC among BE patients has been reported to range between 0.3-0.6% (25).The longer the length of the esophagus affected by BE (e.g. short segment vs. long segment) the higher risk for EAC (26).

## 1.2 Description of the interventions

There are four main modality categories for managing and/or treating among the conditions of interest (stage 1 EAC, BE, dysplasia). These management strategies may overlap among some of the conditions. For example, proton pump inhibitor drugs (PPIs) are not a treatment for EAC but may be used to reduce the risk of developing dysplasia and EAC in persons with BE. In addition, management/treatment strategies may also be used in combination (e.g., pharmacological therapy and surveillance procedures for BE.).

1. Pharmacological therapies, such as:
    a. PPI therapy
    b. H2 receptor antagonists
    c. Cyclo-oxygenase-2 inhibitors
    d. Prokinetics and antacids
    e. Non-steroidal anti-inflammatory drugs (NSAIDs)

2. Surveillance (primarily diagnostic procedures to enhance early detection):
    a. High-definition/high-resolution white light endoscopy
    b. Chromoendoscopy
    c. Electronic chromoendoscopy
    d. Autofluorescence imaging
    e. Confocal laser endomicroscopy
    f. Light scattering spectroscopy, diffuse reflectance spectroscopy

3. Endoscopic or Endoscopic Assisted therapies:
    a. Ablative techniques (eliminate all dysplastic mucosa)
        i. Thermal: Argon plasma coagulation (APC), Multipolar electrocoagulation (MPEC), Radiofrequency ablation (RFA), Cryotherapy/cryoablation, Laser ablation
        ii. Chemical: Photodynamic therapy (PDT)
    b. Mechanical methods (remove targeted superficial tissue of the GI tract)
        i. Endoscopic mucosal resection (EMR)
        ii. Endoscopic submucosal dissection (ESD)
        iii. Combined options (i.e. EMR + PDT, PDT + PPI)

4. Surgery
    a. Laparoscopic anti-reflux surgery (i.e. fundoplication)
    b. Esophagectomy

## 1.3 How interventions might work

Treatments for BE with low- or high-grade dysplasia are intended to control GERD symptoms, heal mucosal inflammation, manage dysplasia, and prevent progression to adenocarcinoma (8).

Pharmacological interventions, such as PPI, work to manage and improve symptoms of GERD by decreasing the production of stomach acid, thereby helping to reduce acid reflux-related symptoms and allowing for healing (27). Surveillance strategies, such as high-definition/high-resolution white light endoscopy and chromoendoscopy, aim to assist in the detection of dysplastic and malignant lesions in persons with known BE and to monitor their progression. These techniques involve various technologies to facilitate visualization and early detection of lesions (4,28). Endoscopic therapy techniques aim to destroy diseased tissue and encourage the growth of new healthy tissue in the esophagus. These various treatment approaches may be combined, depending on the level of dysplasia.

Treatments for EAC are dependent on the stage of cancer (stage 0 to stage 4). Stage 0 disease is considered precancerous and is synonymous with high grade dysplasia wherein abnormal cells are found in the inner layer of cells lining the esophagus but not the deeper layers (29). At this stage endoscopic treatments (e.g., photodynamic therapy) are usually used, followed by surveillance. Stage 1 disease can be treated with EMR and is usually followed by an ablative endoscopic procedure to destroy any remaining abnormal areas in the esophagus lining (29). Stages 2-4 may involve surgical procedures, chemotherapy, radiation, or a combination of these, and are not considered in this review.

### 1.4 Objective

The objective is to provide the CTFPHC with evidence on treatment options for stage 1 EAC and precancerous conditions (BE and/or dysplasia), using an overview of reviews approach. This evidence will be used as indirect evidence for their guideline on screening adults (≥18 years) with chronic GERD with or without other risk factors for EAC and associated precancerous lesions.

### 1.5 Key Question

*What is the effectiveness (benefits and harms) of treatment for stage 1 EAC and precancerous conditions (BE and low- and high-grade dysplasia) in adults?"*

## 2. Methods

This overview of reviews will identify evidence on treatment of stage 1 EAC, BE, and low- and high-grade dysplasia through a systematic search for existing systematic reviews on the topic. As the CTFPHC methods manual does not cover methodology for overview of reviews, the methodology for this overview is based on the *Cochrane Handbook of Systematic Reviews of Interventions (Chapter 22)* (30), and other recent publications that report on overview methods (31,32,33,34,35). Many of the methodological attributes of an overview of reviews are the same as for a SR (e.g., *a priori* inclusion and exclusion criteria, pre-specified search strategies), with some additional considerations to be made (e.g., overlap, scope, synthesizing the results).

Considerations will be made for the following (32,33,34,35):

(i) **Overlap between reviews** (primary studies appearing more than once): If a review is determined to be superseded by a more comprehensive, up-to-date and methodologically rigorous review, this review will be excluded (33). These exclusions will be reported in a table of characteristics of excluded reviews. If there are multiple reviews that are included that contain overlap in the included primary studies (e.g., a review focussing on treatment for BE published in 2015 and a review looking at treatment for BE with no, low-, and high-grade dysplasia and EAC published in 2013), and a formal synthesis is performed, we will address overlap using the corrected covered area (CCA), which is a validated method to calculate the degree of overlap in an overview (32). In the cases of inconsistent data (where information differs for a primary study between reviews), these will be highlighted in the results table.

(ii) **Scope of systematic reviews** (i.e., scope mismatch): For example, if a SR includes people with EAC who did and did not have alarm symptoms and disaggregated information is not provided. SRs with scope mismatch will be excluded, as the information cannot be meaningfully used.

(iii) **Reviews are out of date**: Updating existing systematic reviews will not be performed, as this adds complexity in deciding how to apply inclusion/exclusion criteria (32), and would require additional searching and effort to include those primary studies that add considerable time and resources to complete.

(iv) **Definition of a SR**: To be defined as a SR, a review must meet all of the four following criteria: (1) searches at least one database; (2) reports their selection criteria; (3) conducts quality or risk of bias assessment on included studies; and (4) provides a list and synthesis of included studies.

(v) **Evaluating the methodological quality of the SRs:** This is covered in section 2.5.

(vi) **Evaluating the methodological quality of included research**: As authors of SRs may use differing methodologies, these differences will be reported and considered in making conclusions. The quality assessment tool used by authors to evaluate the primary studies within each SR will be reported in the table of characteristics of included reviews.

(vii) **Evaluating the quality of evidence within SRs**: This is covered in section 2.6.

(viii) **Potential for publication bias**: This may be discussed narratively, but no formal statistical test will be performed (unless provided by the authors of the SRs).

(ix) **Synthesizing and reporting the results of included SRs**: This is covered in section 2.7.

The PRISMA-P guideline (36) was used to develop this protocol (**Appendix 1**). The protocol will be registered in PROSPERO and posted in the Open Science Framework.

## 2.1 Criteria for considering reviews for inclusion

A narrative of the inclusion and exclusion criteria is provided below and the PICOS (Population, Interventions, Comparison, Outcomes, Study design) table can be found in **Appendix 2**.

### *2.1.1 Participants*

We will consider reviews that include participants who are adults (≥18 years) with stage 1 EAC or the precancerous condition of BE and/or low- or high-grade dysplasia. We will not use any predefined method for diagnosis (e.g., histopathological exams, ICD code), and leave it open to how this is defined within each review.

For the purposes of this overview, and where applicable, the presence of underlying chronic GERD will be deemed as per the review authors' definitions, whether reported or not.

SRs with participants who have been diagnosed with other gastroesophageal conditions will be excluded, unless the information is disaggregated from those without other conditions.

### *2.1.2 Interventions*

Reviews must examine the effectiveness of management/treatment strategies for stage 1 EAC or precancerous conditions (BE, low- or high- grade dysplasia), including: 1) pharmacological therapies; 2) surveillance methods; 3) endoscopic or endoscopic assisted therapies;and 4) surgery. Any additional relevant treatment approaches not listed (**Appendix 2**) will be considered for inclusion.

### *2.1.3 Comparisons*

Comparisons of interest include no management/treatment or any other management/treatment strategies or combination of management/treatment strategies.

### *2.1.4 Outcomes*

We will only assess outcomes considered by the CTFPHC EAC working group as critical and important for decision making. These outcomes were drawn from the CTFPHC EAC working group rating and validated with patients as part of the systematic review on the effectiveness of screening for EAC (37).

*Primary/critical outcomes*: All-cause mortality and EAC-related mortality (1, 5, 10 years, or as available), survival (1, 5, 10 years, or as available), progression from non-dysplastic BE to BE with dysplasia, progression from low-grade to high-grade dysplasia, progression to EAC, life threatening or medically significant consequences (e.g., requiring/prolonging hospitalization).

*Secondary/important outcomes*: Quality of life (validated scales only), major or minor medical procedures, psychological effects (e.g., anxiety, stress), overtreatment.

### *2.1.5 Study design*

Systematic reviews of randomized controlled trials (RCTs) that are published in peer-reviewed journals or grey literature, including pre-prints. SRs that include observational studies may be included if results from RCTs are provided separately from observational studies.

## 2.2 Search methods for identification of reviews

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we will search

Ovid MEDLINE®, Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Embase Classic + Embase. We will also search the Cochrane Library on Wiley.

The search strategy can be found in **Appendix 3**. The search strategy will be peer-reviewed using the PRESS 2015 guideline (38). Unpublished literature will be searched, using the CADTH Grey Matters checklist to search for unpublished literature (39).The CADTH checklist includes national and international health technology assessment agencies, clinical practice guideline organizations, drug and device regulatory agencies, health economics resources, systematic review protocol registries, search engines, and databases. The totality of these supplemental searches will be confined to what can be accomplished within 40 hours of work by one team member.

Searches for primary studies published since the date of last search of the SRs included in the overview will not be undertaken.

## 2.3 Selection of reviews

The results from the search strategies will be uploaded into a reference management software. The duplicates will be removed, and the citations will be uploaded into the online SR management software, DistillerSR (40).

Selection of included reviews will be performed in two phases. In phase 1, two reviewers will assess titles/abstracts for eligible systematic reviews, using the liberal accelerated method. This method optimizes screening, where a reference is passed through to the next level of screening if one reviewer deems it potentially relevant. References must be deemed irrelevant by two reviewers for it to be excluded at this level. Screening will be performed independently. Records deemed eligible for inclusion based on titles/abstract will be retrieved in full-text for phase 2 review by two independent reviewers. At full-text review, disagreements will be resolved via discussion and consensus and if needed, a third reviewer. A pilot testing phase among reviewers will be implemented on a sample of records before the commencement of titles/abstracts and full-text review. Questions for both phases of screening will be nested, so that if a record is excluded on a question, the subsequent question will not appear.

Full-text articles that are not available electronically will be ordered via interlibrary loan. For articles that are not received within 30 days, we will exclude and report this as the reason for exclusion. A list of potentially relevant on-going reviews will be provided as an appendix.

Details on the number of reviews included and excluded including the reasons for exclusion will be tracked and recorded in a PRISMA diagram (41). **Appendix 4** provides draft screening questions at both phases of review.

## 2.4 Data extraction and management

Data will be extracted by one reviewer using a data extraction form developed *a priori*. A second reviewer will verify all data. Discrepancies will be resolved with discussion and consensus and if needed, a third reviewer. If unclear whether a review meets the eligibility, the review will be excluded.

We will extract data on the characteristics of the SR (PICO), the included studies with specifics related to the study design, population (e.g., sex, age), outcomes (including definitions and timing of assessment), quality/risk of bias (by domain/construct if available), the methods of analysis, results including subgroup analysis and GRADE or other quality assessments if performed across studies, and any limitations noted by the systematic review authors or by the overview research team.

We will extract data at face value for how it was synthesized and/or reported in the included reviews. No additional information from primary studies will be extracted or assessed, such as outcome data or performing risk of bias assessments, nor will we conduct any quality control to verify the accuracy of the reviews' data extractions or risk of bias assessments for their included studies. If the review information does not allow for clean data extraction we will extract the relevant items and provide a commentary of the review.

### 2.5 Assessment of methodological quality of included reviews

The quality of included reviews will be assessed by one reviewer using the AMSTAR measurement tool (42) (**Appendix 5**). A second reviewer will perform verification on all studies. Any discrepancies in ratings will be resolved through discussion and if needed, a third reviewer.

### 2.6 Quality of evidence in included reviews

The CTFPHC endorses the use of GRADE methodology (1,43) to assess the quality of evidence. GRADE assessments include the consideration of five domains: 1) risk of bias; 2) imprecision; 3) indirectness; 4) inconsistency; 5) publication bias. These elements are used to provide a transparent assessment of the quality of the evidence, from high quality to very low quality.

There are currently no methods to evaluate the strength of findings across different SRs, and some GRADE criteria are only applicable to primary studies (32). GRADE will be done according to the intervention/comparisons of each individual review, but will not be done across reviews, which may mean that if one review assesses a broader grouping of an intervention, it would overlap with a GRADE table from another review that addresses a subset. These results will not be integrated but will be commented on in the text. If available, we will provide results for GRADE using the summary of findings tables provided in each review and their reasons for downgrading for each outcome.

If GRADE methods were not used in the included reviews, we will attempt to conduct GRADE assessments using any available information in the reviews (e.g., risk of bias assessments). Since this is likely difficult to do based on reporting, we will provide our best interpretation based on information that is available and note limitations/cautions. If not possible to perform GRADE assessments, we will report this in the overview. If GRADE is not provided in an included SR, primary studies will not be sought to extract and evaluate information to develop GRADE tables.

We will not conduct any quality control checks to verify the accuracy of the selected reviews' quality of evidence assessments.

### 2.7 Evidence synthesis

The presentation of results will be organized according to the scope of disease being treated and by intervention. A narrative summary of each included review will be provided including:

- Characteristics of the included reviews;
- AMSTAR quality assessments;
- Summary of the quality of evidence within each review and by outcome using GRADE, if available;
- Review findings, summarized in narrative and/or tabular form. Results will be summarized according to early versus late treatment strategies or by stage of EAC or precursor.

The characteristics of each review will be examined closely (e.g., participants, interventions) in order to group similar reviews for comparison and summary of results; such comparisons would assess only the extent of concordance or discordance of the reviews' results and not combine reviews together per se. Where discordance occurs, we will explore reasons for discordance using the Jadad (1997) framework as a guide (44), in addition to any other considerations that may be apparent. Synthesis of the evidence will be presented in such a way to avoid inappropriate indirect comparisons of the evidence, which can only be done properly with network meta-analyses, and in light of content overlap (where applicable), limitations, and other considerations (e.g., reporting issues) of the included SRs.

## 3. Planned schedule and timeline

- Final protocol: February 2018
- List of draft included reviews to WG: February 2018
- GRADE tables to WG, if applicable: May 2018
- Draft report to WG: June 2018
- Final report to WG: August 2018*

*Can be extended to September 28, 2018 if additional time is needed by GHGD to coordinate internal and external review in light of the summer vacation period.

## 4. References


[1] CTFPHC. Canadian task force on preventive health care: Procedure manual. March 2014; Available at: http://canadiantaskforce.ca/methods/.

[2] Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2010. Toronto, ON: Canadian Cancer Society; 2010.

[3] Otterstatter MC, Brierley JD, De P, Ellison LF, McIntyre M, Marrett LD, Semenciw R, Weir HK. Esophageal cancer in Canada: Trends according to morphology and anatomical location. *Can J Gastroentrerol* 2012 Oct; 26(10):723-727.

[4] Sami SS, Subramanian V, Butt WM, Bejkar G, Coleman J, Mannath J, et al. High definition versus standard definition white light endoscopy for detecting dysplasia in patients with Barrett's esophagus. Dis Esophagus 2015 Nov-Dec;28(8):742-749

[5] Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015 Jul 14;21(26):7933-7943

[6] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006 May 10;24(14):2137-2150.

[7] Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111(1):30-50.

[8] Alberta Health Services. Management of patients with early esophageal cancer, dysplastic and non-dysplastic Barrett's esophagus: Clinical Practice Guideline. 2014; Available at: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gi011-barretts-esophagus.pdf. Accessed June 28, 2017

[9] BC Provincial Health Authority, BC Cancer. Esophageal and Esophagogastic Junction Cancer Management Guideline. Available at: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines/gastrointestinal/esophageal-esophagogastric-junction#Treatment-Options-by-Stage. Accessed: December 11, 2017.

[10] Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P, et al. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2012 Dec 04;157(11):808-816

[11] Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology 2011 Mar;140(3):1084-1091

[12] National Institute for Health and Care Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management: Clinical guideline. 2014; Available at: https://www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-in-adults-investigation-and-management-pdf-35109812699845. Accessed June 21, 2017.

[13] Fernando HC, Murthy SC, Hofstetter W, Shrager JB, Bridges C, Mitchell JD, Landreneau RJ, Clough ER, Watson TJ; Society of Thoracic Surgeons. The Society of Thoracic Surgeons practice guideline series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. *Ann Thorac Surg* 2009 Jun; 87(6):1993-2002.

[14] Ajani JA, Barthel JS, Bentrem DJ, D'Amico TA, Das P, Denlinger CS, et al. Esophageal and Esophagogastric Junction Cancers. *J Natl Compr Canc Netw* 2011; 9:830-887.

[15] Canadian Cancer Society, Symptoms of Esophageal Cancer. Available at: http://www.cancer.ca/en/cancer-information/cancer-type/esophageal/signs-and-symptoms/?region=on. Accessed: December 11, 2017

[16] Wani S, Drahos J, Cook MB, Rastogi A, Bansal A, Yen R, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. Gastrointest Endosc 2014 Feb;79(2):224-232

[17] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, and the Global Consensus Group. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. *American Journal of Gastroenterology* 2006; 101:1900-1920.

[18] Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults - update 2004. Can J Gastroenterol 2005 Jan;19(1):15-35

[19] Fedorak RN, Veldhuyzen van Zanten S, Bridges R. Canadian Digestive Health Foundation Public Impact Series: gastroesophageal reflux disease in Canada: incidence, prevalence, and direct and indirect economic impact. Can J Gastroenterol 2010 Jul;24(7):431-434.

[20] Sharma P, Falk GW, Sampliner R, Jon Spechler S, Wang K. Management of nondysplastic Barrett's esophagus: where are we now? Am J Gastroenterol 2009 Apr;104(4):805-808

[21] Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med 2014 Aug 28; 371(9):836-845.

[22] Veldhuyzen van Zanten,S J O., Thomson ABR, Barkun AN, Armstrong D, Chiba N, White RJ, et al. The prevalence of Barrett's oesophagus in a cohort of 1040 Canadian primary care patients with uninvestigated dyspepsia undergoing prompt endoscopy. Aliment Pharmacol Ther 2006 Mar 01;23(5):595-599

[23] Runge TM, Abrams JA, Shaheen NJ. Epidemiology of Barrett's Esophagus and Esophageal Adenocarcinoma. Gastroenterol Clin North Am 2015 Jun;44(2):203-231.

[24] Sikkema M, de Jonge PJF, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clinical Gastroenterology & Hepatology 2010;8(3):235-244

[25] Schoofs N, Bisschops R, Prenen H. Progression of Barrett's esophagus towards esophageal adenocarcinoma: an overview. *Annals of Gastroenterology* 2017: 30(1):1-6.

[26] Pohl H, Pech O, Arash H, Stolte M, Manner H, May A, et al. Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. Gut 2016 Feb;65(2):196-201.

[27] El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2004 Oct; 99(10):1877-1883.

[28] Trivedi PJ, Braden B. Indications, stains and techniques in chromoendoscopy. *QJM* 2013 Feb; 106(2):117-131

[29] American Cancer Society. Treating Esophageal Cancer by Stage. 2017; Available at: https://www.cancer.org/cancer/esophagus-cancer/treating/by-stage.html. Accessed June, 2017.

[30] Higgins, JPT, Green, S (editors). The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. March 2011; Available at: http://training.cochrane.org/handbook. Accessed June 28, 2017.

[31] McKenzie JE, Brennan SE. Overviews of systematic reviews: great promise, greater challenge. *Systematic Reviews* 2017; 6:185.

[32] Ballard M, Montgomery P. Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist. *Research Synthesis Methods* 2017 Mar; 8(1): 92-108.

[33] Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: implications from five exemplar overviews. *Syst Rev* 2017; 6:145.

[34] Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. *Syst Rev* 2016; 5:190.

[35] Hartling L, Vandermeer B, Fernandes RM. Systematic reviews, overviews of reviews and comparative effectiveness reviews: a discussion of approaches to knowledge synthesis. *Evidence-Based Child Health: A Cochrane Review Journal* 2014; 9:486-494.

[36] Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M. et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;*349.*

[37] Hamel C, Beck A, Stevens A, Skidmore B, Chatterjee A, James P, et al. Effectiveness of screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: protocol for a systematic review. PROSPERO: CRD42017049993. 2017; Available at: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017049993. Accessed June 22, 2017.

[38] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016 Jul;75:40-46

[39] The Canadian Agency for Drugs and Technologies in Health (CADTH). Grey Matters: a practical search tool for evidence-based medicine. 2015; Available at: https://www.cadth.ca/resources/finding-evidence/grey-matters. Accessed June 20, 2017.

[40] Evidence Partners. Distiller (DistillerSR systematic review software) computer program. Ottawa, ON; 2017.

[41] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009;3(3):e123-30

[42] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D,Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;15(7):10.

[43] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004 Jun 19;328(7454):1490

[44] Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *CMAJ* 1997; 156(10):1411-1416.

## Appendix 1: PRISMA-P checklist

| Section and topic | Item No | Checklist item | Reported on page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| **Title:** | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | n/a |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 1 (once registered) |
| **Authors:** | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1-2 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 2 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | n/a |
| **Support:** | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 2 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | 2 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | 2 |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 3 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 6 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 8-9, Appendix 2 (18-19) |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 9 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Appendix 3 (20-22) |
| **Study records:** | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 9-10 |
| Selection | 11b | State the process that will be used for selecting studies (such as two | 9 |

| | | | |
|---|---|---|---|
| process | | independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 10 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 10 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Appendix 2 (18) |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 10 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 11 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 11 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | n/a |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 11 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 7 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 10-11 |

## Appendix 2: Population, Intervention, Comparison, Outcomes (PICOs)

| | Inclusion | Exclusion |
|---|---|---|
| **Population** | Adults (≥18 years old) with stage 1 EAC, BE, or low- or high-grade dysplasia, with or without chronic GERD as defined in the systematic reviews. | Those diagnosed with other gastro-esophageal conditions. |
| **Interventions** | Treatment for stage 1 EAC, low- or high-grade dysplasia or BE including:<br>1. Pharmacological therapies such as: PPI, H2 receptor antagonists, Cox-2 inhibitors, Prokinetics and antacids, NSAIDs;<br>2. Surveillance methods such as: Esophagogastroduodenoscopy (EGD)*† plus biopsy[‡], EGD† plus biopsy plus adjunct techniques‡ (high-definition/high-resolution white light endoscopy, chromoendoscopy, electronic chromoendoscopy, autofluorescense imaging, confocal laser endomiscroscopy, light scattering spectroscopy, diffuse reflectance spectroscopy;<br>3. Endoscopic or Endoscopic Assisted therapies such as: Ablative techniques (thermal or chemical), and mechanical methods (EMR, ESD or combined options)<br>4. Surgery, including fundoplication and esophagectomy | Any follow-up diagnostic tests, such 24 hour esophageal pH test or any test for staging purposes, such as CT and MRI |
| **Comparators** | No management/treatment compared to another management/treatment regimen | |
| **Outcomes** | 1. Mortality - all-cause and EAC-related (1, 5 and 10 year, or as available)†<br>2. Survival (1, 5 and 10 year, or as available)†<br>3. Progression from non-dysplastic BE to BE with dysplasia, progression from low-grade to high-grade dysplasia, progression to EAC<br>4. Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living)<br>5. Quality of life (validated scales only; e.g. SF-36, WHOQUAL)<br>6. Major or minor medical procedures<br>7. Psychological effects (e.g., anxiety, stress)<br>8. Overtreatment<br><br>†from the time of allocation to screening or control arm | |
| **Timing** | No limits | |
| **Settings** | Any setting | |
| **Study designs** | Systematic reviews of randomized controlled trials (RCTs)*<br><br>*Systematic reviews that combine RCT and non-RCTs will be included if results for RCTs are provided separately from non-RCT studies. | SRs that combine results from RCTs with non-RCTs, controlled before-after, interrupted times series, cohort studies, case-control studies, cross-sectional studies, case series, case reports, and |

| | Inclusion | Exclusion |
|---|---|---|
| | | other publication types (editorials, commentaries, notes, letter, opinions) or SRs that only include non-RCT and observational studies. |
| **Language** | No language restrictions in the search, however only English articles will be included at full-text. | |
| **Databases** | Medline, Embase, Cochrane (CDSR, DARE, HTA) | |

**Also known as panendoscopy and upper GI endoscopy

† Biopsy may be included

‡ For example, chromendoscopy and narrow-band imaging

ƪ biopsy may not be necessary in all cases

# Appendix 3: Search Strategy

Barrett's/Esophageal Cancer - Reviews
Updated 2017 Dec 6

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2017 December 05>, Ovid MEDLINE(R) ALL <1946 to December 05, 2017>
Search Strategy:
---

1 Barrett Esophagus/ (22629)
2 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasi* or syndrome?)).tw,kf. (22105)
3 1 or 2 (26954)
4 ((Barrett* or esophag* or oesophag* or pharynx-esophag* or gastro-esophag* or gastro-oesophag*) adj3 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kf. (5811)
5 3 or 4 (28176)
6 Esophageal Neoplasms/ (55882)
7 exp Esophagus/ and exp Neoplasms/ (36277)
8 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kf. (113247)
9 or/6-8 (142370)
10 5 or 9 (154891)
11 exp Infant/ not (exp Adult/ and exp Infant/) (1671699)
12 exp Child/ not (exp Adult/ and exp Child/) (3177575)
13 10 not (11 or 12) (153709)
14 exp Animals/ not (exp Animals/ and Humans/) (15777336)
15 13 not 14 (122422)
16 (comment or editorial or interview or news).pt. (1828845)
17 (letter not (letter and randomized controlled trial)).pt. (2033865)
18 15 not (16 or 17) (117104)
19 limit 18 to systematic reviews [Limit not valid in Embase; records were retained] (55564)
20 meta analysis.pt. (95504)
21 exp meta-analysis as topic/ (55666)
22 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf. (302696)
23 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kf. (354412)
24 exp Technology assessment, biomedical/ (23396)
25 (cochrane or health technology assessment or evidence report).jw. (35410)
26 (network adj (MA or MAs)).tw,kf. (15)
27 (NMA or NMAs).tw,kf. (3901)
28 indirect* compar*.tw,kf. (4267)
29 (indirect treatment* adj1 compar*).tw,kf. (545)
30 (mixed treatment* adj1 compar*).tw,kf. (1251)
31 (multiple treatment* adj1 compar*).tw,kf. (296)
32 (multi-treatment* adj1 compar*).tw,kf. (3)
33 simultaneous* compar*.tw,kf. (2140)
34 mixed comparison?.tw,kf. (41)
35 or/20-34 (636227)
36 18 and 35 (2474)

37 19 or 36 (55826)
38 37 use medall [MEDLINE RECORDS] (2079)
39 Barrett esophagus/ (22629)
40 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasi* or syndrome?)).tw,kw. (22478)
41 39 or 40 (27136)
42 esophagus dysplasia/ (771)
43 exp esophagus/ and dysplasia/ (1569)
44 ((Barrett* or esophag* or oesophag* or pharynx-esophag* or gastro-esophag* or gastro-oesophag*) adj3 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kw. (5891)
45 or/42-44 (7272)
46 41 or 45 (28738)
47 exp esophagus tumor/ (73959)
48 exp esophagus/ and exp neoplasm/ (36277)
49 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kw. (113450)
50 or/47-49 (149139)
51 46 or 50 (161194)
52 exp juvenile/ not (exp juvenile/ and exp adult/) (2259851)
53 exp Infant/ not (exp Adult/ and exp Infant/) (1671699)
54 exp Child/ not (exp Adult/ and exp Child/) (3177575)
55 or/52-54 (3910277)
56 51 not 55 (159863)
57 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47895779)
58 exp human/ or exp human experimentation/ or exp human experiment/ (37527300)
59 57 not 58 (10370199)
60 56 not 59 (156324)
61 editorial.pt. (1026593)
62 letter.pt. not (letter.pt. and randomized controlled trial/) (2029082)
63 60 not (61 or 62) (150308)
64 meta-analysis/ (233981)
65 "systematic review"/ (157820)
66 "meta analysis (topic)"/ (37994)
67 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw. (305331)
68 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw. (357272)
69 biomedical technology assessment/ (22257)
70 (cochrane or health technology assessment or evidence report).jw. (35410)
71 (network adj (MA or MAs)).tw,kw. (15)
72 (NMA or NMAs).tw,kw. (3920)
73 indirect* compar*.tw,kw. (4321)
74 (indirect treatment* adj1 compar*).tw,kw. (548)
75 (mixed treatment* adj1 compar*).tw,kw. (1263)
76 (multiple treatment* adj1 compar*).tw,kw. (299)
77 (multi-treatment* adj1 compar*).tw,kw. (3)
78 simultaneous* compar*.tw,kw. (2140)
79 mixed comparison?.tw,kw. (42)
80 or/64-79 (687966)
81 63 and 80 (4540)
82 81 use emczd [EMBASE RECORDS] (3014)

83 38 or 82 [BOTH DATABASES] (5093)
84 remove duplicates from 83 (3405) [TOTAL UNIQUE RECORDS]
85 84 use medall [MEDLINE UNIQUE RECORDS] (1695)
86 84 use emczd [EMBASE UNIQUE RECORDS] (1710)

**********

## Appendix 4: Draft screening forms

| Phase 1: Title and abstract screening questions | Answer‡ |
|---|---|
| **Intervention:** Does the review describe a management/treatment regimen for EAC and/or BE and/or low- or high-grade dysplasia? (i.e., pharmacological, surveillance, surgical/mechanical or chemotherapy/radiation, surgery)? | ❍ Yes/unclear<br>❍ No |
| **Study design**: Is this reference a review (addresses multiple studies within)? (exclude primary studies such as RCTs, cohort, case-control, cross-sectional, case series, case reports, and editorials/ commentaries/ opinion pieces) | ❍ Yes/unclear<br>❍ No |
| **Population:** Does the review discuss adults (≥18 years)? | ❍ Yes/unclear<br>❍ No |

‡ Yes/unclear: include; No: exclude

| Phase 2: Full-text screening questions | Answer† |
|---|---|
| **Study Design:** Is the paper a systematic review?<br>Must meet all of the following criteria: 1) searched at least one database; 2) reported selection criteria; 3) reported quality appraisal; 4) provided a list and synthesis of included studies. | ❍ Yes<br>❍ No<br>❍ Unclear |
| **Population:** Does the review include adults (≥18 years)? (or disaggregated information if combined with those <18 years old or where >80% of the population are adults) | ❍ Yes<br>❍ No<br>❍ Unclear |
| **Population:** Does the review discuss those with stage 1 EAC, BE, low or high grade dysplasia? | ❍ Yes<br>❍ No<br>❍ Unclear |
| **Intervention:** Does the review evaluate a management/treatment regimen for stage 1 EAC and/or BE and/or low- or high-grade dysplasia? (i.e., pharmacological, surveillance, surgical/mechanical or chemotherapy/radiation, surgery)? | ❍ Yes<br>❍ No<br>❍ Unclear |
| **Comparison:** Does the review compare one management/treatment strategy to another management/treatment strategy or to no management/treatment? | ❍ Yes<br>❍ No<br>❍ Unclear |
| **Outcome**: Does the review evaluate one of the outcomes of interest? (i.e., mortality, survival, incidence of stage 1 EAC, BE, low- and high-grade dysplasia, life threatening, severe, or medically significant consequences, QoL, major or minor medical procedures, psychological effects, overtreatment) | ❍ Yes<br>❍ No<br>❍ Unclear |

† Yes: include; No: exclude; Unclear: follow-up with WG/clinical experts

## Appendix 5: AMSTAR checklist

| | |
|---|---|
| **1. Was an 'a priori' design provided?**<br>The research question and inclusion criteria should be established before the conduct of the review.<br>*Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **2. Was there duplicate study selection and data extraction?**<br>There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.<br>*Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **3. Was a comprehensive literature search performed?**<br>At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.<br>*Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?**<br>The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.<br>*Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **5. Was a list of studies (included and excluded) provided?**<br>A list of included and excluded studies should be provided.<br>*Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **6. Were the characteristics of the included studies provided?**<br>In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.<br>*Note: Acceptable if not in table format as long as they are described as above.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **7. Was the scientific quality of the included studies assessed and documented?**<br>'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.<br>*Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **8. Was the scientific quality of the included studies used appropriately in** | ❒ Yes |

| | |
|---|---|
| **formulating conclusions?**<br>The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.<br>*Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.* | ❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **9. Were the methods used to combine the findings of studies appropriate?**<br>For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, $I^2$). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).<br>*Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **10. Was the likelihood of publication bias assessed?**<br>An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).<br>*Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |
| **11. Was the conflict of interest included?**<br>Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.<br>*Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.* | ❒ Yes<br>❒ No<br>❒ Can't answer<br>❒ Not applicable |

*Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.*