

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 series of systematic reviews

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Candyce Hamel,^a Andrew Beck,^a Adrienne Stevens,^a Becky Skidmore,^b Avijit Chatterjee,^{ac} Paul James,^{cd} Donna Maziak,^{cd} Lise M Bjerre,^d Ian Coleman,^d Beverley Shea,^a Kednapa Thavorn,^a Brian Hutton,^{ad} Micere Thuku,^a Doreen Whelan,^a Julian Little*,^d David Moher*.^{ad} Patient values and preferences in relation to screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus): protocol for a systematic review.

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Author contribution:

AS, CH, and AB drafted the protocol. BS developed the search strategy and provided text for the protocol. JL, DM, BJS, BH, KT critically reviewed the protocol and provided methodological expertise. PJ, AC, DM, LMB, and IC reviewed the protocol and provided clinical expertise for the review.

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The funder will provide feedback on the draft systematic review, but will not be involved in a publication decision.

Chapter I. Purpose and Background

This protocol outlines knowledge syntheses that will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to inform a guideline on screening adults (≥ 18 years) with chronic gastroesophageal reflux disease (GERD) with or without other risk factors for esophageal adenocarcinoma (EAC) and associated precancerous lesions. The forthcoming reviews will synthesize evidence on the benefits, harms, and patient values and preferences for screening in this population.

Definition and burden of esophageal adenocarcinoma

Esophageal cancer is a disease where malignant cells form in the tissues of the esophagus. Two primary types of esophageal cancer exist: esophageal adenocarcinoma (EAC; with 46% of global cases occurring in Northern and Western Europe, Northern American and Oceania) and esophageal squamous cell carcinoma (ESCC; with 79% of global cases occurring in South-Eastern and Central Asia) [Arnold 2015]. ESCC is the most frequent type of esophageal cancer in Asian countries, while EAC is more commonly found in North America and Europe [Domper Arnal 2015]. The incidence of EAC in Canada has doubled in the past 20 years, while a decline has been observed for ESCC [Otterstatter 2012]. Given the geographic distribution of subtypes and increasing incidence of EAC in Canada, the focus of the guideline will be on EAC.

Esophageal cancer has a lower incidence than other cancers, but a high mortality rate. In Canada, esophageal cancer is the thirteenth most common cancer in men and nineteenth most common in women, but the sixth and fourteenth most common cause of cancer deaths, respectively [Canadian Cancer Society 2015]. In 2015 there were an estimated 2,200 cases of esophageal cancer newly diagnosed in Canada, and 2,100 deaths from the disease [Canadian Cancer Society 2015]. Between 1986 and 2006, the incidence of EAC in Canada increased from 1.8 to 3.5 per 100,000 in men, and 0.2 to 0.5 per 100,000 in women; with projected increases of 40% in men and 50% in women by 2026 [Otterstatter 2012].

Risk factors for esophageal adenocarcinoma

Commonly cited risk factors for EAC are chronic gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), age ≥ 50 years, male sex, European descent, obesity, smoking, a family history of BE or EAC, and a diet low in fruits and vegetables [Domper Arnal 2015; Otterstatter 2012; Kamangar 2006; Shaheen 2016].

Gastroesophageal reflux disease (GERD) is one of the most commonly encountered conditions in primary care practice with an estimated prevalence of between 18-27% in the United States and 8.8%-25.9% in Europe [El-Serag 2014]. Extrapolating this to the Canadian population would mean that 3.4-6.8 million persons in Canada would be experiencing GERD [Fedorak 2010]. GERD is a chronic disease with varying criteria for a standard definition, however, many have adopted the Montreal definition, "a condition which develops when the reflux of stomach contents causes troublesome symptoms (e.g., retrosternal burning (heartburn), regurgitation) and/or complications (e.g., esophagitis, esophageal stricture)" [Shaheen 2012; Fedorak 2010; Kahrilas 2008; Jones 2005]. Furthermore, various definitions exist for chronic GERD [Hirota 2006; Anvari 2011; Grant 2013; Mahon 2005]. According to the American Society for Gastrointestinal Endoscopy, chronic, long-standing GERD is defined as experiencing frequent severe GERD symptoms for over five years and requiring regular acid suppression therapy [Hirota 2006]. However, studies differ in regards to the duration of symptoms and acid suppression therapy [Anvari

2011; Grant 2013; Mahon 2005]. In order to maintain broad inclusion criteria and in consideration of existing definitions of chronic GERD, this review will define chronic GERD as: 1) symptoms of GERD for 12 months or more with no specific frequency; and/or 2) proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for 12 months or more.

The most common complications of GERD are esophagitis, esophageal stricture, BE (a premalignant lesion, further described below), and EAC [Fedorak 2010]. However, even among individuals experiencing GERD symptoms, the risk of EAC is quite low; further, roughly 40% of people with EAC have no prior history of GERD [Spechler 2014; Locke 1997]. Patients with GERD could also experience possible alarm symptoms, such as chest pain, dysphagia, odynophagia (painful swallowing), vomiting, gastrointestinal blood loss, weight loss, that are indicative of more serious conditions [Marchetti 2009].

Treatment options for chronic GERD involve long-term administration of an acid suppression therapy such as proton pump inhibitors (PPI) and/or surgical therapy [Ip 2011]. Surgical treatment has been shown to be as effective as medical therapy for patients with chronic GERD [Katz 2013], although it shows little long-term advantage over medical therapy. Although endoscopic treatments exist, they are not recommended as alternative to medical or surgical therapies [Ip 2011; Katz 2013].

BE, a premalignant lesion, is known to develop in around 6%-14% of people with GERD, and among those with BE, 0.5%-1% develop EAC [Wheeler 2012]. However, not all individuals with BE will experience chronic GERD symptoms, and it is still unclear why such a small percentage of people with GERD develop BE [Gorospe 2014; Weijenborg 2016]. Once an individual is diagnosed with BE, surveillance may be considered as BE can progress over time from low to high-grade dysplasia and into EAC [Eloubeidi 2001; Lao-Sirieix 2012].

Screening for esophageal adenocarcinoma and precancerous conditions

The components of a successful screening program include the following key criteria: (1) the burden of disease is such that it warrants a screening program; (2) the disease has a preclinical phase that a screening test can detect; (3) there is a clinical intervention that targets the preclinical phase of the disease; (4) the clinical intervention improves outcomes (most importantly, mortality); and (5) the screening program is cost effective [Dellon 2005]. Based on these key criteria, there have been advocates for and against a screening program for EAC and precancerous conditions. In cost-utility modelling, one-time screening in Caucasian men with symptoms of GERD at the age of 50 years, followed by surveillance of those found to have BE with dysplasia, may be cost-effective, whereas surveillance of those found to have BE but no dysplasia exceeded generally accepted thresholds for cost-effective care [Inadomi 2003]. In addition, endoscopic surveillance in patients with BE has shown statistically significant survival advantage in patients with cancers detected by endoscopic surveillance [Strayer 2011]. However, there are also several shortcomings of surveillance programs for EAC and precancerous conditions: there is low risk of progression to cancer, 40% of patient with EAC do not have reflux symptoms, and dysplasia may not be visible through endoscopy. In addition, patients should be counseled about the risks and benefits of surveillance [Dellon 2005; Shaheen 2016].

In Canada, the gold standard in clinical practice to screen for EAC and precancerous conditions is to perform an endoscopy of the upper gastrointestinal tract (esophagogastroduodenoscopy (EGD)). If lesions or anomalies consistent with BE, dysplasia and possible EAC are found, a tissue biopsy is performed with targeted 4-quadrant biopsies every 1-2 cm along the length of the BE (called the Seattle Protocol); this is considered the gold standard in diagnosing EAC [Domper Arnal 2015; Pennathur 2013]. Several adjunct techniques exist, such as chromoendoscopy, narrowband imaging, confocal microscopy,

spectroscopy, magnification endoscopy, and high definition endoscopy to aid in the detection of early stage cancer [ASGE 2013]. Other existing screening technologies include barium swallow, transnasal ultrathin endoscopes, cytologic examination (brush, balloon, sponge, liquid), and capsule endoscopy, many of which are emerging technologies that are not currently used in Canadian clinical practice. Furthermore, new methods for screening such as flow cytometry, molecular biomarkers, and laser-induced fluorescence spectroscopy have been proposed for use in screening, but are currently only being assessed in a research setting.

In Canada, endoscopy of the upper GI tract is widely available and routinely performed for the diagnosis and management of long standing GERD or BE, their complications, and esophageal cancer [Otterstatter 2012; Sonnenberg 2008]. With Canada's aging population, there is an expected increase in GERD and EAC, and, therefore, increased demand for gastrointestinal endoscopies [Fedorak 2010; Leddin 2013]. Between 2004 and 2008, the number of upper endoscopies performed in Canada had increased by approximately 16% [Armstrong 2012].

Endoscopy screening is not without risk. While one-time endoscopy is considered to be a safe procedure with low risks of complications, it is an uncomfortable and invasive procedure that is costly, requires sedation, requires special expertise, and exposes the patient to procedure-related risks [Breslin 2000]. Experiencing multiple endoscopies carries the potential risks of cardiopulmonary complications from sedation and analgesia, infection, perforation, and excessive bleeding [Ben-Menachem 2012], without improving positive outcomes, and thus contributes to potentially unnecessary health care costs [Shaheen 2012].

Recommendations from Other Guideline Developers

Currently, there are no known national recommendations on screening for esophageal cancer in Canada. The province of Alberta has a provincial guideline for the screening and management of BE and early esophageal cancer. There are also recommendations focused on the management of GERD and BE, including the 2004 Canadian Association of Gastroenterology (CAG) consensus statement on management of GERD based on expert opinion [Armstrong 2005]. Although it is not a screening guideline, many Canadian primary care physicians refer to the Compendium of Therapeutic Choices for guidance [Canadian Pharmacists Association 2014].

We are aware that the following organizations outside of Canada have released guidelines on endoscopic screening for esophageal cancer, including information on screening people diagnosed with GERD: the American College of Physicians (ACP) [Shaheen 2012], the American Gastroenterological Association (AGA) [Spechler 2011], and the National Institute for Health and Care Excellence [NICE 2015]. The ACP has also developed a guideline for best practices in individuals with BE [Shaheen 2016].

There is a general consensus among the CAG, ACP, and AGA against screening the general population with GERD for EAC and BE. Screening is not seen as an appropriate first step in most patients presenting with only GERD symptoms [Shaheen 2012; Spechler 2011]. However, there is a consensus on screening males 50 years and older who are suffering from chronic GERD symptoms (defined as symptoms for more than five years [Shaheen 2012; Spechler 2011] or ten years [Armstrong 2005]) and who have additional risk factors for EAC (European descent, nocturnal reflux symptoms, hiatal hernia, high body mass index, large waist circumference (abdominal obesity), and tobacco use [Shaheen 2012; Spechler 2011; Armstrong 2005; Steffen 2015]).

The ACP and NICE provide information on screening individuals with alarm symptoms; however this population subgroup would be considered different from that of interest to the proposed guideline. The

ACP and NICE guidelines further recommend routine screening in men and women with heartburn and alarm symptoms (i.e., dysphagia, bleeding, anemia, weight loss, and recurrent vomiting), individuals who experience GERD symptoms or severe erosive esophagitis after four to eight weeks of PPI therapy, or who have a history of esophageal stricture with recurrent symptoms of dysphagia [Shaheen 2012; NICE 2015].

Current Practice

In Canada, GERD is managed through acid suppression therapy, most commonly with PPI, but could also be managed with histamine-2 receptor antagonists (H2RAs), or antacids for infrequent symptoms. An alternative to medical therapy in long-term GERD in selected patients is surgical anti-reflux surgery, although it shows little long-term advantage over medical therapy. Endoscopy to detect BE with dysplasia is used in adults with long-standing GERD and other risk factors. If BE is confirmed, PPI therapy is continued in addition to endoscopic surveillance with biopsy at different intervals, depending on the level of dysplasia.

Objective

The CTFPHC is undertaking a systematic evaluation of the evidence to inform its recommendations for primary healthcare in Canada in the area of esophageal adenocarcinoma, as: 1) incidence of EAC is increasing in Western countries; 2) EAC has a high mortality and is usually diagnosed at an advanced stage; 3) there are common risk factors identifiable in primary care that could translate into a risk calculator for screening of BE, dysplasia, and early stage EAC; 4) some estimates indicate that 2.4%-13.2% of patients with GERD who are undergoing endoscopy will develop BE; 5) BE with dysplasia is one pathway to the development of EAC, although there are other possible pathways; 6) behavioural preventive interventions (e.g., tobacco cessation) can be undertaken; 7) interventions are available for patients with BE that may prevent EAC; and 8) treatment of early EAC may increase survival [Wheeler 2012; Schweigert 2013; Spechler 2014; El-Serag 2015; Torre 2016; Alderson 2016; Kuipers 2011].

The series of planned systematic reviews will provide a synthesis of the benefits, harms, and patient values and preferences in relation to screening for EAC and precancerous conditions (dysplasia and BE) in adults with chronic GERD with or without other risk factors.

These reviews are not designed to evaluate the association between different severities of GERD (mild, moderate, and severe) and progression to EAC. Rather the specific objective is to evaluate the potential benefits of screening in a defined high-risk group, individuals with chronic GERD, who can be identified with some consistency in primary care practice.

Chapter 2. Methods Overview

These reviews will be completed by the Evidence Review and Synthesis Centre (ERSC) at the Ottawa Hospital Research Institute. These reviews will be developed, conducted, and prepared according to the CTFPHC Procedure Manual [CTFPHC 2014] or as methods are updated by the Task Force. A working group of CTFPHC members was formed for development of the topic, refinement of the key questions and scope, and rating of patient-important outcomes considered most important for creating a recommendation. Perspectives of patients will be incorporated regarding prioritization of outcomes (benefits and harms). This protocol was prepared in accordance with the PRISMA-P guidelines [Moher 2015] (**Appendix A**), and once finalized, methods for the various questions will be posted on the CTFPHC website and registered with the International Prospective Registry of Systematic Reviews (PROSPERO) database (PROSPERO #s).

The reviews will be reported according to the PRISMA statement [Moher 2009], and will include a PRISMA flow diagram. We will also use the conduct reported in a Measurement Tool to Assess the Methodological Quality of Systematic Reviews (AMSTAR) tool for additional quality control [Shea 2007].

No work outlined within this protocol updates any previously conducted systematic review. Any amendments made to this protocol when conducting the reviews will be outlined in the related review's manuscript.

Figure 1: Analytic Framework for EAC Screening

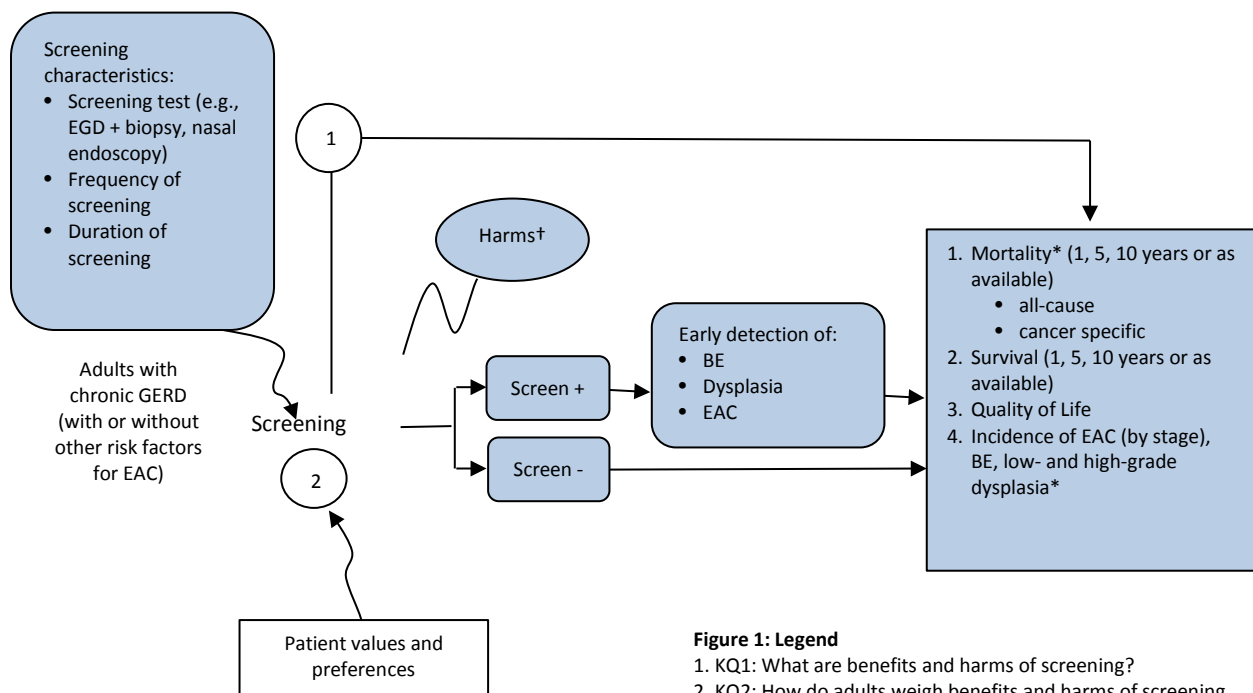


Figure 1: Legend

1. KQ1: What are benefits and harms of screening?
2. KQ2: How do adults weigh benefits and harms of screening (patient preferences)?

†Harms of screening

- Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living)
- Psychological effects (i.e., anxiety and depression)
- Major or minor medical procedures*
- Overdiagnosis†

‡ Outcomes with * will be used to calculate overdiagnosis

Key Questions

Two evidence syntheses will be conducted. The first will focus on synthesizing the evidence on the effectiveness of screening for BE, dysplasia, and EAC. For the effectiveness of screening question, we will begin with randomized controlled trials. If no or few randomized controlled trials are available, we may consider evidence from other study designs (e.g., non-randomized controlled clinical trials, cohort studies, case-control studies), acknowledging their limitations as more biased evidence; accordingly, we will focus on higher levels of evidence where available. We will also be evaluating patient preferences and values of screening for EAC.

Quality of evidence (classified as high, moderate, low, very low) will be assessed using methods developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (<http://www.gradeworkinggroup.org/>).

Decisions made during the evidence review are based on the information needs of the CTFPHC for making a screening recommendation based on the balance of critical patient-important benefits and harms. The decision to include observational evidence will be approved by the CTFPHC and will be properly documented.

Although there is no consensus on a definition for chronic GERD, for the purposes of these knowledge syntheses, chronic GERD will be defined as (1) symptoms for ≥ 12 months, with no specific frequency; and/or (2) proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for ≥ 12 months.

KQ1a (Chapter 3): In adults with chronic GERD with or without other risk factors[†], what is the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and low- and high-grade dysplasia)? What are the effects in relevant subgroup populations?

[†]Risk factors will be deemed so by included studies

KQ1b (Chapter 3): If there is evidence of effectiveness[†], what is the optimal time to initiate and to end screening, and the optimal screening interval (includes single and multiple tests and ongoing 'surveillance')?

[†]If there is evidence of at least moderate quality of evidence, according to GRADE

KQ2 (Chapter 4): In adults with chronic GERD with or without other risk factors who have been offered, received, or allocated to receive screening, how do they weigh the benefits and harms of screening, and what factors contribute to these preferences and to their decisions to undergo screening?

General Methodology for Systematic Reviews

Inclusion/exclusion, literature search, and data analysis information specific to each question can be found in subsequent chapters.

Study Selection

There will be no language or date restrictions in the search. Duplicates across searches will be identified and removed using Reference Manager [Reuters T 2011]. The remaining articles will be uploaded into an online systematic review managing software, Distiller Systematic Review (DistillerSR) Software© [Partners E 2011] for broad screening (Level 1) and more precisely focused screening of the remaining potential relevant articles (Level 2). Level 1 will consist of two reviewers independently screening for relevance based on title and abstracts. We will use a liberal accelerated method in which a second

reviewer will verify those records deemed not relevant by the first reviewer. As these are done concurrently, each reviewer will not know if the reference has already been reviewed and deemed not relevant. At Level 2, the full-text will be retrieved and two reviewers will independently assess the article for relevancy. Conflicts will be resolved by consensus or a third team member. If chronic GERD is not defined in a study, we will attempt to contact the study authors twice over two weeks by email to obtain more information. If there is no response by authors, the study will be excluded. Reports that are co-publications or multiple reports of the same study will be identified as such. English and French articles will be included at full-text.

The Task Force has developed a list of outcomes and harms, which were ranked according to GRADE methodology. Through consensus, outcomes ranked as critical for decision-making (ranked 7 to 9 out of 9) and important (ranked 4 to 6 out of 9) are included. A maximum of seven outcomes are included for each key question to balance the benefits and harms for guideline panel consideration. In addition, patients will be involved in ranking patient important outcomes.

A pilot testing phase among reviewers will be implemented on a sample of articles prior to commencement of full screening at both level 1 (50 titles and abstracts) and level 2 (typically 20-30 studies, dependent on the yield from level 1). Articles not available electronically will be ordered via interlibrary loan. If the article is not received within 30 days, it will be excluded and unavailability noted as the reason for exclusion.

Reports in abstract form will be noted as such, and a search will be done to see if the full-text is available. A list of potential relevant studies available only in abstract form will be made available. A list of grey literature sources, including registries for on-going or completed studies, will be provided for each question. Clinical and content experts identified by the CTFPHC will be contacted and invited to submit research reports for consideration. We will consult within the CTFPHC and experts for missing studies.

When scanning references of relevant secondary evidence reports for additional studies, evidence-based clinical practice guidelines, systematic reviews, and meta-analyses will be prioritized if a large volume of secondary reports exist and would need to meet the following criteria:

- (i) At least one database was searched;
- (ii) It reports selection criteria;
- (iii) Quality assessment of included studies is reported; and
- (iv) It provides a list and synthesis of included studies.

Where study eligibility is unclear, authors will be contacted by email twice over two weeks for additional information.

Data Extraction and Management

Standardized data extraction forms will be developed *a priori* in DistillerSR and pilot tested on a sample of studies, with this number dependent on the yield of included studies. Full data abstraction will be completed by one reviewer and verified by a second reviewer. Disagreements will be resolved by consensus or third party adjudication if consensus cannot be reached.

Where needed, we will convert data (e.g., standard error to standard deviation) to facilitate consistent presentation of results across studies and for analyses. All formats of continuous outcome data will be extracted whether reported as post-intervention or change from baseline. Where needed, a correlation coefficient of 0.25 will be used to impute standard deviations for means used in change from baseline calculations.

Authors will be contacted by email twice over two weeks if any information is missing or unclear. If no response is received and eligibility cannot be determined through published reports, the study will be excluded.

Risk of Bias Assessment

The risk of bias of included studies will be assessed by one reviewer. Verification will be completed by a second reviewer. Disagreements will be resolved by consensus or third party adjudication. Assessment tools used and other key question-specific details are provided in each Chapter below.

Some domains are outcome-specific and will be assessed at the outcome level. The overall risk of bias for the body of evidence will involve a judgement of the relative importance of domains, guided by known empirical evidence of bias, the likely direction of bias, and the likely magnitude of bias [Higgins 2008]. We will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance for determining the extent of the risk of bias for the body of evidence [Balshem 2011]. For outcome and analysis reporting bias, we will use the methods outlined in the AHRQ guidance to determine risk of bias for that domain [Balshem 2013]. Some tools may need to be adjusted, depending on the study design; for example, when assessing cluster randomized trials, we would assess for the possibility of recruitment bias in the 'other bias' domain of the Cochrane risk of bias tool [Higgins 2011].

Planned Schedule and Timeline

Draft protocol to WG: July 13, 2016

Final protocol: December 23, 2016

Draft GRADE table(s): June 9, 2017

Draft evidence review: October 31, 2017

Final evidence review: December 20, 2017

Draft recommendation statement: April 2018

Submit for publication: July 2018

Chapter 3. Effectiveness of Screening on Clinical and Patient Important Outcomes: Protocol for Systematic Review

Research Questions

KQ1a. In adults with chronic GERD with or without other risk factors[†], what is the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and low- and high-grade dysplasia)? What are the effects in relevant subgroup populations?

[†]Risk factors will be deemed so by included studies

KQ1b. If there is evidence of effectiveness[‡], what is the optimal time to initiate and to end screening, and the optimal screening interval (includes single and multiple tests and ongoing ‘surveillance’)?

[‡] If there is evidence of at least moderate quality of evidence, according to GRADE

Inclusion and Exclusion Criteria

Studies will be selected according to the inclusion and exclusion criteria outlined below.

Table 1 – Inclusion and exclusion criteria for key question 1a&b

	Inclusion	Exclusion
Population	<p>Adults (≥18 years old) with chronic GERD with or without other risk factors[†] for EAC</p> <p>Studies addressing both adults and children, if data provided for adults are reported separately</p> <p>Definition of chronic GERD: (1) symptoms for ≥12 months, with no specific frequency; and/or (2) proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for ≥12 months[‡]</p> <p>[†] Risk factors will be as deemed so by included studies [‡] Some studies may report the population of interest as a subgroup; we will extract this information accordingly. We will include studies where the population includes 20% or less of patients who do not meet our definition of chronic GERD.</p>	<p>Experiencing alarm symptoms for EAC: dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as ‘alarm’</p> <p>Diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC)</p>
Intervention and comparator – KQ1a	<p>All screening modalities will be included, such as:</p> <ul style="list-style-type: none"> - Esophagogastroduodenoscopy (EGD)*[†] - EGD[†] plus adjunct techniques[‡] - Transnasal endoscopy - Cytologic examination <p>*Also known as panendoscopy and upper GI endoscopy [†] with or without biopsy protocol [‡]For example, chromendoscopy and narrow-band imaging</p> <p>Screening for BE, dysplasia, or EAC</p>	<p>Any follow-up diagnostic tests, such 24 hour esophageal pH test or any test for staging purposes, such as CT and MRI</p>
Intervention and comparator – KQ1b	<ul style="list-style-type: none"> - One screening modality vs. another screening modality 	

	<ul style="list-style-type: none"> - One interval of screening vs. another interval of screening - Timepoint at which to initiate screening vs. another timepoint - Timepoint at which to cease screening vs. another timepoint 	
Outcomes/Outcome domains	<p>Critical for decision-making</p> <ol style="list-style-type: none"> 1. Mortality - all-cause and cancer-related (1, 5 and 10 year or as available)†* 2. Survival (1, 5 and 10 year or as available)† 3. Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living) <p>Important for decision-making</p> <ol style="list-style-type: none"> 4. Incidence of EAC (by stage), BE, low- and high-grade dysplasia* 5. Quality of life (validated scales only; e.g. SF-36, WHOQUAL) 6. Psychological effects (e.g., anxiety and depression) 7. Major or minor medical procedures* 8. Overdiagnosis‡ <p>†from the time of allocation to screening or control arm *These outcomes will be used to judge the extent of overdiagnosis, which is defined as the diagnosis of disease which would never have become clinically apparent in a person's lifetime (i.e., causing neither symptoms nor death). ‡As judged by the study author or will be judged by the CTFPHC working group using information provided by authors, where available.</p>	
Timing	No limits	
Settings	Primary care	
Study designs	<p>Randomized controlled trials (RCTs), including cluster RCTs.</p> <p>If no or few randomized controlled trials (i.e. less than 5 trials) are available: Non-randomized controlled clinical trials, controlled before-after, interrupted times series, cohort studies, case-control studies, limiting to higher levels of evidence depending on the nature and volume of specific study designs.</p> <p>If no or few randomized controlled trials are available for the overdiagnosis outcome, ecological and cohort studies will be considered for all outcomes used for the judgment of</p>	Cross-sectional studies, case series, case reports, and other publication types (editorials, commentaries, notes, letter, opinions).

	overdiagnosis.	
Language	No language restrictions in the search, however only English and French articles will be included at full-text.	
Databases	Medline, Embase, Cochrane	

CT: computerized tomography; MRI: magnetic resonance imaging

Literature Search

The search strategy will be 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.

Strategies will utilize a combination of controlled vocabulary (e.g., “Gastroesophageal Reflux”, “Esophageal Neoplasms”, “Endoscopy”) and keywords (e.g., “GERD”, “esophageal cancer”, “esophagoscopy”). Vocabulary and syntax will be adjusted across databases. When possible, animal-only and opinion-pieces will be removed from the results.

The draft search strategy for KQ1 can be found in **Appendix B**. The final search will be peer-reviewed using the PRESS 2015 guideline [McGowan 2016].

We will use the CADTH Grey Matters checklist to search for unpublished literature and search the following websites: the Canadian Association of Gastroenterology, the Canadian Digestive Health Foundation, the Ontario Association of Gastroenterology, the American Society for Gastrointestinal Endoscopy, the American College of Gastroenterology, the American Gastroenterological Association, the British Society of Gastroenterology, the American College of Physicians, Cancer Care Ontario, BC Cancer Agency, Alberta Health Care Services, the Canadian Cancer Society, the American Cancer Society, US Preventive Services Task Force, the Agency for Healthcare Research Quality, and the Centres for Disease Control and Prevention. Grey literature searching will be confined to what can be accomplished within one week. In addition, we will scan the bibliographies of relevant reviews and clinical practice guidelines. We will search ClinicalTrials.gov, the ISRCTN trial register, and the World Health Organization’s International Clinical Trials Registry Platform for ongoing or completed studies.

Study Selection

Details of the study selection process can be found in Chapter 2, under the Study Selection section. Draft example level 1 and 2 screening forms are shown in **Appendix C**.

Data Extraction and Management

Details for the data extraction and management process can be found in Chapter 2, under the Data Extraction and Management section. Draft items for data extraction can be found in **Appendix D**.

Risk of Bias Assessment

Details for the risk of bias assessment process can be found in Chapter 2, under the Risk of Bias Assessment section. Assessments will feed into the GRADE domain of study limitations. The Cochrane Risk of Bias tool [Higgins 2008] (**Appendix E**) will be used to evaluate the risk of bias in randomized controlled trials.

Should other study designs be included, we will use the following risk of bias tools: the Cochrane risk of bias tool for controlled clinical trials (**Appendix E**), the EPOC tool for controlled before-after studies (**Appendix F**), the Newcastle-Ottawa scale [Wells 2000] will be used to evaluate the risk of bias in cohort (**Appendix G**) and case-control (**Appendix H**) studies, and the EPOC tool will be used for interrupted time series studies (**Appendix I**).

Analysis Plan

Study characteristics will be summarized narratively and presented in summary tables. Where possible, relative and absolute effects with 95% confidence intervals will be calculated to facilitate presentation according to the GRADE summary of findings and evidence profile tables adopted by the CTFPHC. For example, risk ratios and risk differences will be ideally used to report effects for binary data. GRADE guidance will be used for presenting continuous data [Guyatt 2013]. Where possible, the number needed to treat/harm will be calculated.

Due to the increase in the number of people being screened and the technological advancement of the screening tests, overdiagnosis in cancer is occurring. Overdiagnosis is defined as the diagnosis of disease which would never have become clinically apparent in a person's lifetime (i.e., causing neither symptoms nor death) [Welch HG 2010]. This could happen because the cancer never progresses, or because the cancer progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic. Quantifying overdiagnosis is challenging, as it would need to include modeling the natural history of the cancer, the impact of early diagnosis, and competing mortality. Seven different methods of calculating overdiagnosis have been proposed [Marmot 2013]. The method used to calculate overdiagnosis will be determined based on the available information in the included studies.

Meta-analysis. Before proceeding with a meta-analysis, we will determine whether clinical and methodological heterogeneity exists among studies. If appropriate, data will be meta-analyzed, using random effects models. Should meta-analysis not be appropriate, the range of effects will be presented. For time-to-event data, the hazard ratio will be pooled using the generic inverse variance method. One notable consideration is the groupings of risk factors (e.g., age ≤ 50 years vs > 50 years compared to age deciles elsewhere) which may vary across the studies included in the review; a decision may need to be made post hoc as to how data from subgroups reported in variable formats will be handled. Where possible, results will be sex-disaggregated. Analyses would be stratified into logical study classifications, should evidence other than RCTs be included; for example, we would meta-analyze RCTs and CCTs together, and keep cohort studies separate.

If observational studies are included, use of adjusted estimates of effect (and their corresponding listings of confounders which were modeled), will be an important criterion to evaluate for heterogeneity. Ideally, adjusted estimates will be used in the meta-analysis.

Unit of analysis errors can occur in studies that employ a cluster design (e.g., a clinical practice) and yet are analyzed at the individual level (e.g., patients), potentially leading to overly precise results and contributing greater weight in a meta-analysis. If empirically-derived intracluster correlation coefficients (ICC) are available, we will adjust the analysis to address these errors [Killip 2004]. For multiple events that may occur in one person (e.g., adverse events), we will assume each event represents a unique individual, unless otherwise specified. If we were to encounter a study where there is reason for concern that many events are recorded but likely in a small % of patients, these could be evaluated in sensitivity analyses.

Sparse binary data and studies with zero events. When studies report rare events, a narrative synthesis will be performed. For those outcomes (e.g. serious adverse events) where at least one intervention group contains zero events, only the risk difference will be used. For calculating the RD, we will use the median baseline risk for the control group in the included studies, although may perform sensitivity analysis using differing baseline risks if thought suitable.

Statistical heterogeneity. The Cochrane's Q (considered statistically significant at $p < 0.10$) and I^2 statistic will be used to assess the statistical heterogeneity of effect estimates amongst included studies. For the interpretation of I^2 , a rough guide of low (0-25%), moderate (25-50%), substantial (50%-75%), and considerable ($\geq 75\%$) will be used [Higgins 2003; Sterne 2011]. Should considerable statistical heterogeneity exist, we will present all studies in a forest plot, but will not provide the pooled estimate. When the body of evidence is statistically heterogeneous, we will conduct subgroup, sensitivity analysis, and/or meta-regression analyses, where the optimal approach for each variable will be determined once we see how data are reported in studies. We will follow previously published guidance for meta-regression [Fu 2011]. Meta-regression will be based on random effects models to allow for residual unexplained heterogeneity. A p value < 0.10 will characterize statistical significance. When the sizes of the included studies are moderate or large, there should be at least 10 studies for a continuous study-level variable. For a categorical subgroup variable, each subgroup should have a minimum of four studies. These numbers serve as the lower bounds for considering meta-regression [Fu 2011]. When included studies are mostly small in size, univariate meta-regression will be used when an insufficient number of studies are available to conduct multivariable analyses.

Sub-group analyses. The following subgroup analyses are planned:

- Age (<50 years, ≥ 50 years)
- Sex
- BMI, waist circumference or other measures of obesity
- Smoking history
- Duration of chronic GERD (determined post-hoc based on included studies)
- Definition of chronic GERD by study authors
- Groupings of risk factors (will be determined post hoc, depending on combination of risk factors as reported in studies)
- Various ethnic groups, including Indigenous people (will be determined post hoc, depending on populations encountered in studies)
- Rural versus urban settings

Sensitivity analyses. Sensitivity analyses may be undertaken to restrict analyses to those studies assessed as being of low risk of bias, based on the overall judgment, and may also be performed to address any decisions made regarding handling of data or to explore statistical heterogeneity. A sensitivity analysis may also be performed on the timing of publication, based on cut-offs as determined by literature.

Small study effects. To assess for small study effects, a combination of graphical aids (e.g. funnel plot) and/or statistical tests (e.g., Egger regression test, Hedges-Olkin) will be performed subject to at least 10 studies in the analysis.

Software. The Cochrane Review Manager software version 5.3 [RevMan 2014] will be used to calculate effect estimates and conducting meta-analyses. For all analyses not possible in RevMan, we will use Comprehensive Meta-Analysis (CMA) or Stata.

Grading the quality of evidence and interpretation. For critical and important outcomes, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [GRADE Working Group 2004; CTFPHC Procedure Manual 2014] will be used to assess the quality of the evidence.

Chapter 4. Patient Values and Preferences of Screening: Protocol for Systematic Review

Research Question

KQ2. In adults with chronic GERD with or without other risk factors who have been offered, received, or allocated to receive screening, how do they weigh the benefits and harms of screening, and what factors contribute to these preferences and to their decisions to undergo screening?

Inclusion and Exclusion Criteria

Studies will be selected according to the inclusion and exclusion criteria outlined below.

Table 1 – Inclusion and exclusion criteria for key question 2

	Inclusion	Exclusion
Population	<p>Adults (≥18 years old) with chronic GERD with or without other risk factors[†] for EAC who have been offered, received, or allocated to receive screening, depending on the design of the study</p> <p>Studies addressing both adults and children, if data provided for adults are reported separately</p> <p>Definition of chronic GERD: (1) symptoms for ≥12 months, with no specific frequency; and/or (2) proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for ≥12 months[‡]</p> <p>[†] We will include studies where the population includes 20% or less of patients who do not meet our definition of chronic GERD.</p> <p>[‡] Risk factors will be as deemed so by included studies.</p>	<p>Experiencing alarm symptoms for EAC: dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as ‘alarm’</p> <p>Diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC)</p>
Interventions	Screening for EAC and other precancerous lesions with any screening modality	Any follow-up diagnostic tests, such as 24 hour esophageal pH test or any test for staging purposes, such as CT and MRI
Comparators	<p>Depending on study design, comparators may be:</p> <ul style="list-style-type: none"> - No screening* - Different screening modality - Different screening intervals - Different lengths/duration of screening - Offered screening but did not receive screening - No comparison <p>*Although we will consider comparative studies that include a no screening arm, we understand that the outcomes of interest do not apply to people who do not receive or have not been offered screening. For such studies, we will only consider data for those who receive or are offered screening.</p>	
Outcomes	<ul style="list-style-type: none"> - Willingness to be screened - Uptake of screening - Factors considered in decision to be screened: what 	

	<p>components/outcomes of screening do patients place more value on when deciding whether to be screened or not (e.g. potential complications resulting from screening)</p> <ul style="list-style-type: none"> - Intrusiveness of the screening modality 	
Timing	No limits	
Settings	Primary care or other settings generalizable to primary care	
Study designs	<p>Randomized controlled trials</p> <p>If insufficient data exists: Controlled clinical trials, controlled before-after, case-controls, cohort, interrupted time series (ITS), and cross-sectional (e.g., surveys)</p> <p>If insufficient data exists for the above: Qualitative studies and mixed-methods studies</p>	Commentaries, opinion, editorials, and reviews
Language	No language restrictions in the search. English and French articles will be included at full-text.	
Databases	Medline, Embase, CINAHL, Cochrane	

Literature Search

The search strategy will be 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 CINAHL using the EBSCO platform and the Cochrane Library on Wiley.

Strategies will utilize a combination of controlled vocabulary (e.g., “Gastroesophageal Reflux”, “Patient Acceptance of Health Care”, “Informed Consent”) and keywords (e.g., “GERD”, “patient perspective”, “informed decision-making”). Vocabulary and syntax will be adjusted across databases. When possible, animal-only and opinion-pieces will be removed from the results.

The draft search strategy for KQ2 can be found in **Appendix J**. The final search will be peer-reviewed using the PRESS 2015 guideline [McGowan 2016].

We will use CADTH Grey Matters checklist to search for unpublished literature. We will also search the following websites: the Esophageal Cancer Awareness Association, the Canadian Cancer Society, the American Cancer Society, the American Cancer Association, the Oesophageal Patients Association, the Esophageal Cancer Education Fund, and the Esophageal Cancer Action Network.

Study Selection

Details for the study selection process can be found in Chapter 2, under the Study Selection section.

Data Extraction and Management

Details for the data extraction and management process can be found in Chapter 2, under the Data Extraction and Management section.

Risk of Bias Assessment

Details for the risk of bias assessment process can be found in Chapter 2, under the Risk of Bias Assessment section.

We will use the Cochrane Risk of Bias tool [Higgins 2008] (**Appendix E**) to evaluate the risk of bias in randomized controlled trials. If insufficient data exists in randomized controlled trials, we will use the Cochrane risk of bias tool for controlled clinical trials, the EPOC tool for controlled before-after studies (**Appendix F**), the Newcastle-Ottawa scale [Wells 2000] will be used to evaluate the risk of bias in cohort (**Appendix G**) and case-control (**Appendix H**) studies, and the EPOC tool will be used for interrupted time series studies (**Appendix I**). If applicable, the Critical Appraisal Skills Programme (CASP) Qualitative checklist (**Appendix K**) will be used to critically appraise qualitative studies.

Analysis Plan

The analysis approach will depend on the design of included studies. We will report means and standard deviations, mean differences, and p-values for studies that include validated tools (e.g, SF-36) and will report qualitative themes in narrative format, if applicable.

Meta-analysis. Quantitative data will be meta-analyzed, using random effects models, as appropriate, depending on the similarity of study characteristics and the risk of bias of studies. Should meta-analysis not be appropriate, the range of effects will be presented. Single-arm studies will use a two-phase approach stating first with a narrative of findings. Next, we would look across studies to determine consistency of reporting of outcomes to determine whether quantitative analyses (e.g., pooling) is possible.

Synthesis of qualitative studies. Should qualitative studies be included, results will be combined according to the thematic synthesis approach [Thomas 2008]. Results or findings from each qualitative study will be extracted and entered into Microsoft Excel. Data synthesis will involve line-by-line coding of the results from each study, organization of codes into descriptive themes, and the development of analytical themes [Thomas 2008].

Mixed-methods synthesis. Should both quantitative and qualitative study designs be included, results will be synthesized according to the result-based convergent synthesis design [Pluye 2013]. Using this approach, results from qualitative and quantitative studies are synthesized separately. We will then combine the results into an overall synthesis [Pluye 2013].

Sensitivity analysis. A sensitivity analysis may also be performed on the timing of publication, based on cut-offs as determined by literature.

Software. The Cochrane Review Manager software version 5.3 [RevMan 2014] will be used to calculate effect estimates and conduct meta-analyses. Microsoft Excel will be used to manage, code, and synthesize qualitative data.

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Appendix A. 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	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1 (PROSPERO registration after protocol approved by Working Group)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
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	7
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	3-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-8
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	11-12, 16-17, 19-20, Tables 1-3
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	8-9, 12-13, 17, 20
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	29-35
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
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	9
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	9, 38, 56
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9, 12, 16, 20
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, 13, 17-18, 21
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	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 τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13-14, 18, 21
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7, 10, 13, 15, 18

Appendix B. Search Strategy for Key Question 1: Effectiveness of Screening

Database: Embase Classic+Embase <1947 to 2016 November 21> , Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

- 1 exp Gastroesophageal Reflux/ (79539)
- 2 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (56206)
- 3 GERD.tw,kw. (20579)
- 4 GORD.tw,kw. (2011)
- 5 SEGR.tw,kw. (15)
- 6 (gastric adj2 regurgitat*).tw,kw. (482)
- 7 or/1-6 (93727)
- 8 Esophageal Neoplasms/ (55261)
- 9 exp Esophagus/ and exp Neoplasms/ (40051)
- 10 ((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. (104411)
- 11 Barrett Esophagus/ (21823)
- 12 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasi* or syndrome?)).tw,kw. (21384)
- 13 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw. (222900)
- 14 or/8-13 (357636)
- 15 7 and 14 [GERD AND ESOPHAGEAL CANCER] (13391)
- 16 exp Infant/ not (exp Adult/ and exp Infant/) (1626948)
- 17 exp Child/ not (exp Adult/ and exp Child/) (3104242)
- 18 15 not (16 or 17) [CHILD-ONLY REMOVED] (12937)
- 19 exp Animals/ not (exp Animals/ and Humans/) (16258536)
- 20 18 not 19 [ANIMAL-ONLY REMOVED] (9516)
- 21 (comment or editorial or interview or news).pt. (1759710)
- 22 (letter not (letter and randomized controlled trial)).pt. (1940264)
- 23 20 not (21 or 22) [OPINION PIECES REMOVED] (8979)
- 24 limit 23 to systematic reviews [Limit not valid in Embase; records were retained] (4959)
- 25 meta analysis.pt. (81202)
- 26 exp meta-analysis as topic/ (53170)
- 27 (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. (254188)
- 28 (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. (298759)
- 29 exp Technology assessment, biomedical/ (22334)
- 30 (cochrane or health technology assessment or evidence report).jw. (35484)
- 31 or/25-30 (543350)
- 32 23 and 31 (200)
- 33 24 or 32 [REVIEWS] (4995)
- 34 exp Guidelines as Topic/ (548535)
- 35 exp Clinical Protocols/ (234769)
- 36 Guideline.pt. (16984)
- 37 Practice Guideline.pt. (23567)
- 38 standards.fs. (655615)
- 39 Consensus Development Conference.pt. (11147)
- 40 (guidance* or guideline* or standards or recommendation*).ti. (284534)
- 41 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (101508)
- 42 or/34-41 (1540435)
- 43 23 and 42 [GUIDELINES] (314)
- 44 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (560003)
- 45 clinical trials as topic.sh. (189500)
- 46 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1871292)
- 47 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (356754)
- 48 trial.ti. (399402)
- 49 or/44-48 (2342120)
- 50 23 and 49 [RCTS] (437)
- 51 controlled clinical trial.pt. (95071)
- 52 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (561524)

53 (control* adj2 trial*).tw. (464527)
54 Non-Randomized Controlled Trials as Topic/ (10613)
55 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (98162)
56 (nRCT or nRCTs or non-RCT\$1).tw. (1256)
57 Controlled Before-After Studies/ (275072)
58 (control* adj3 ("before and after" or "before after")).tw. (7997)
59 Interrupted Time Series Analysis/ (259131)
60 (time series adj3 interrupt*).tw. (3824)
61 (pre- adj3 post-).tw. (159890)
62 (pretest adj3 posttest).tw. (8533)
63 Historically Controlled Study/ (294274)
64 (control* adj2 stud\$3).tw. (448379)
65 Control Groups/ (276369)
66 (control\$ adj2 group\$1).tw. (978533)
67 trial.ti. (399402)
68 or/51-67 (2834582)
69 23 and 68 [NON-RCTS] (895)
70 exp Cohort Studies/ (2015266)
71 cohort\$1.tw. (1062753)
72 Retrospective Studies/ (889285)
73 (longitudinal or prospective or retrospective).tw. (2373231)
74 ((followup or follow-up) adj (study or studies)).tw. (105340)
75 Observational study.pt. (30168)
76 (observation\$2 adj (study or studies)).tw. (177212)
77 ((population or population-based) adj (study or studies or analys#s)).tw. (33393)
78 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (220)
79 Comparative Study.pt. (1882119)
80 ((comparative or comparison) adj (study or studies)).tw. (217534)
81 exp Case-Control Studies/ (1016246)
82 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (195940)
83 Cross-Sectional Studies/ (318067)
84 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey\$1)).tw. (351337)
85 or/70-84 (6620343)
86 23 and 85 [OBSERVATIONAL STUDIES] (2308)
87 33 or 43 or 50 or 69 or 86 [ALL STUDY DESIGNS] (6694)
88 87 use ppez (1878)
89 gastroesophageal reflux/ (71875)
90 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (56206)
91 GERD.tw,kw. (20579)
92 GORD.tw,kw. (2011)
93 SEGR.tw,kw. (15)
94 (gastric adj2 regurgitat*).tw,kw. (482)
95 or/89-94 (87194)
96 exp esophagus tumor/ (69467)
97 exp esophagus/ and exp neoplasm/ (40051)
98 ((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. (104411)
99 Barrett Esophagus/ (21823)
100 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome?)).tw,kw. (21384)
101 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw. (222900)
102 or/96-101 (360504)
103 95 and 102 [GERD AND ESOPHAGEAL CANCER] (12488)
104 exp juvenile/ not (exp juvenile/ and exp adult/) (2215665)
105 exp Infant/ not (exp Adult/ and exp Infant/) (1626948)
106 exp Child/ not (exp Adult/ and exp Child/) (3104242)
107 or/104-106 (3795161)
108 103 not 107 [CHILD, 17 AND UNDER, REMOVED] (12039)
109 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (45646611)
110 exp human/ or exp human experimentation/ or exp human experiment/ (35807107)
111 109 not 110 (9841229)
112 108 not 111 [ANIMAL-ONLY REMOVED] (11727)
113 editorial.pt. (967331)
114 letter.pt. not (letter.pt. and randomized controlled trial/) (1935021)
115 112 not (113 or 114) [OPINION PIECES REMOVED] (11104)
116 meta-analysis/ (233958)

117 "systematic review"/ (146008)
118 "meta analysis (topic)"/ (36207)
119 (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. (254188)
120 (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.
(298759)
121 biomedical technology assessment/ (21182)
122 (cochrane or health technology assessment or evidence report).jw. (35484)
123 or/116-122 (588496)
124 115 and 123 [REVIEWS] (420)
125 exp practice guideline/ (429217)
126 (guidance* or guideline* or standards or recommendation*).ti. (284534)
127 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy
statement* or CPG or CPGs).tw. (101508)
128 or/125-127 (716029)
129 115 and 128 [GUIDELINES] (368)
130 randomized controlled trial/ or controlled clinical trial/ (1186424)
131 exp "clinical trial (topic)"/ (266257)
132 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1871292)
133 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (356754)
134 trial.ti. (399402)
135 or/130-134 (2599290)
136 115 and 135 [RCTS] (762)
137 controlled clinical trial/ (548342)
138 "controlled clinical trial (topic)"/ (10510)
139 (control* adj2 trial*).tw. (464527)
140 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (98162)
141 (nRCT or nRCTs or non-RCT\$1).tw. (1256)
142 (control* adj3 ("before and after" or "before after")).tw. (7997)
143 time series analysis/ (23769)
144 (time series adj3 interrupt*).tw. (3824)
145 pretest posttest control group design/ (336)
146 (pre- adj3 post-).tw. (159890)
147 (pretest adj3 posttest).tw. (8533)
148 controlled study/ (5326045)
149 (control* adj2 stud\$3).tw. (448379)
150 control group/ (276369)
151 (control* adj2 group\$1).tw. (978533)
152 trial.ti. (399402)
153 or/137-152 (7024072)
154 115 and 153 [NON-RCTS] (1942)
155 cohort analysis/ (535001)
156 cohort\$1.tw. (1062753)
157 retrospective study/ (1159005)
158 longitudinal study/ (227378)
159 prospective study/ (852800)
160 (longitudinal or prospective or retrospective).tw. (2373231)
161 follow up/ (1251862)
162 ((followup or follow-up) adj (study or studies)).tw. (105340)
163 observational study/ (153960)
164 (observation\$2 adj (study or studies)).tw. (177212)
165 population research/ (90510)
166 ((population or population-based) adj (study or studies or analys#s)).tw. (33393)
167 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (220)
168 exp comparative study/ (3090597)
169 ((comparative or comparison) adj (study or studies)).tw. (217534)
170 exp case control study/ (1016246)
171 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (195940)
172 cross-sectional study/ (461144)
173 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey\$1)).tw. (351337)
174 or/155-173 (8317267)
175 115 and 174 [OBSERVATIONAL STUDIES] (3641)
176 124 or 129 or 136 or 154 or 175 [ALL STUDY DESIGNS] (5082)
177 176 use emczd [EMBASE RECORDS] (3398)
178 88 or 177 [BOTH DATABASES] (5276)

179 remove duplicates from 178 (3777) [UNIQUE RECORDS – ALL STUDY DESIGNS]
 180 33 use ppez (179)
 181 124 use emczd (293)
 182 180 or 181 [REVIEWS - BOTH DATABASES] (472)
 183 remove duplicates from 182 [UNIQUE REVIEWS - BOTH DATABASES] (363)
 184 183 use ppez [UNIQUE MEDLINE REVIEWS] (155)
 185 183 use emczd [UNIQUE EMBASE REVIEWS] (208)
 186 43 use ppez (127)
 187 129 use emczd (319)
 188 186 or 187 (446)
 189 188 not 182 (372)
 190 remove duplicates from 189 [UNIQUE GUIDELINES - BOTH DATABASES] (322)
 191 190 use ppez [MEDLINE UNIQUE GUIDELINES] (79)
 192 190 use emczd [EMBASE UNIQUE GUIDELINES] (243)
 193 50 use ppez (244)
 194 136 use emczd (546)
 195 193 or 194 (790)
 196 195 not (182 or 188) (650)
 197 remove duplicates from 196 [UNIQUE RCTS - BOTH DATABASES] (489)
 198 197 use ppez [MEDLINE UNIQUE RCTS] (193)
 199 197 use emczd [EMBASE UNIQUE RCTS] (296)
 200 69 use ppez (425)
 201 154 use emczd (1524)
 202 200 or 201 (1949)
 203 202 not (182 or 188 or 195) (1454)
 204 remove duplicates from 203 [UNIQUE NON-RCTS - BOTH DATABASES] (1179)
 205 204 use ppez [MEDLINE UNIQUE NON-RCTS] (228)
 206 204 use emczd [EMBASE UNIQUE NON-RCTS] (951)
 207 86 use ppez (1548)
 208 175 use emczd (2237)
 209 207 or 208 (3785)
 210 209 not (182 or 188 or 195 or 202) (2328)
 211 remove duplicates from 210 [UNIQUE OBSERVATIONAL STUDIES - BOTH DATABASES] (1801)
 212 211 use ppez [MEDLINE UNIQUE OBSERVATIONAL STUDIES] (979)
 213 211 use emczd [EMBASE UNIQUE OBSERVATIONAL STUDIES] (822)
 214 183 or 190 or 197 or 204 or 211 (4154)
 215 remove duplicates from 214 [VERIFICATION OF TOTAL UNIQUE RECORDS - ALL STUDY DESIGNS – AS PER LINE 179] (3777)

Cochrane Library

Date Run: 22/11/16 17:16:07.375

ID	Search	Hits
#1	[mh "Gastroesophageal Reflux"]	1626
#2	((esophageal or gastric* or (gastro next esophageal) or (gastro next oesophageal) or supraesophageal or (supra next esophageal) or supraoesophageal or (supra next oesophageal)) near/2 reflux*):ti,ab,kw	989
#3	GERD:ti,ab,kw	832
#4	GORD:ti,ab,kw	131
#5	SEGR:ti,ab,kw	0
#6	(gastric near/2 regurgitat*):ti,ab,kw	48
#7	{or #1-#6}	2466
#8	[mh "Esophageal Neoplasms"]	1177
#9	[mh Esophagus] and [mh Neoplasms]	235
#10	((esophag* or oesophag* or (pharynx next esophag*)) near/3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or (adeno next carcinoma*) or carcinosarcoma* or (carcino next sarcoma*))):ti,ab,kw	2666
#11	[mh "Barrett Esophagus"]	237
#12	(Barrett* near/1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome*)):ti,ab,kw	348
#13	(dysplasia* or dysplastic* or precancer* or (pre next cancer*) or premalignan* or (pre next malignan*)):ti,ab,kw	2706
#14	{or #8-#13}	5325
#15	#7 and #14	101
#16	[mh Infant] not ([mh Adult] and [mh Infant])	14615
#17	[mh Child] not ([mh Adult] and [mh Infant])	201
#18	#15 not (#16 or #17)	99

DSR - 5
DARE - 3
CENTRAL - 82
NHS EED - 9

Appendix C. Draft screening forms for KQ1

Level 1 and level 2 example for KQ1. Effectiveness of screening

Level 1 – Title and abstract screening

1. Does this article discuss esophageal cancer, dysplasia or Barrett’s esophagus in individuals with chronic GERD and other risk factors?
 - Yes/unclear***
 - No

*Those answered yes/unclear will be passed through to full-text screening.

Level 2 – Full-text screening

1. Language of publication
 - English or French**
 - Other
2. Is this article a randomized controlled trial/cluster randomized controlled trial?
 - Yes**
 - No
3. Is the population aged ≥ 18 years old (adult population)?
 - Yes**
 - No
 - Mixed (children and adults)**
 - Unclear (contact authors)**
4. If this article includes a mixed population, do they provide adult specific outcomes data?
 - Yes**
 - No
5. Does this article include a relevant intervention?
 - Yes (e.g., EGD, transnasal endoscopy)**
 - No
6. Does this article include a relevant comparator?
 - Yes (e.g., no screening, other test)**
 - No (no comparator)

Typically, these questions are nested. If an answer allows us to proceed in the inclusion criteria, the next question will appear. Those bolded would be those that would pass through to the following question. If question 6 is 'Yes', this article would be passed through to a post-hoc evaluation, ensuring it has outcomes of interest.

Appendix D. Draft items for data extraction for KQ1

Publication details: year of publication, language, publication status

Characteristics of study: study design, methods, country, setting, sample size, number of centres [if applicable], duration of follow-up, source of funding

Characteristics of population: age, sex, ethnicity, other risk factors, information regarding respondent bias/representativeness of the included population

Details about the exposure/intervention: type of screening test performed, frequency/interval of screening

Details about comparator: type of screening test performed (or no screening), frequency/interval of screening (if applicable)

Outcomes of interest: definitions, measurement methods, data, adjusted and unadjusted effect estimates

Confounding factors that were taken into consideration

Risk of bias items

Appendix E. Draft Cochrane Risk of Bias piloting form

1. **Selection bias domain:** Random sequence generation

- Low risk
- Unclear risk
- High risk

Support for judgement:

2. **Selection bias domain:** Allocation concealment

- Low risk
- Unclear risk
- High risk

Support for judgement:

3. **Performance bias domain:** Blinding of participants and personnel (for each outcome)

- Low risk
- Unclear risk
- High risk

Support for judgement:

4. **Detection bias domain:** Blinding of outcome assessment (for each outcome)

- Low risk
- Unclear risk
- High risk

Support for judgement:

5. **Attrition bias domain:** Incomplete outcome data (for each outcome)

- Low risk
- Unclear risk
- High risk

Support for judgement:

6. **Reporting bias domain:** Selective reporting

- Low risk
- Unclear risk
- High risk

Support for judgement:

7. **Other sources of bias**

- Low risk
- Unclear risk
- High risk

Support for judgement:

Appendix F. EPOC risk of bias tool for Controlled Before-After studies

Was the allocation sequence adequately generated?

Score “Low risk” if a random component in the sequence generation process is described (eg Referring to a random number table). Score “High risk” when a nonrandom method is used (eg performed by date of admission). NRCTs and CBA studies should be scored “High risk”. Score “Unclear risk” if not specified in the paper.

Was the allocation adequately concealed?

Score “Low risk” if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used. CBA studies should be scored “High risk”. Score “Unclear risk” if not specified in the paper.

Were baseline outcome measurements similar?

Score “Low risk” if performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups. In RCTs, score “Low risk” if imbalanced but appropriate adjusted analysis was performed (e.g. Analysis of covariance). Score “High risk” if important differences were present and not adjusted for in analysis. If RCTs have no baseline measure of outcome, score “Unclear risk”.

Were baseline characteristics similar?

Score “Low risk” if baseline characteristics of the study and control providers are reported and similar. Score “Unclear risk” if it is not clear in the paper (e.g. characteristics are mentioned in text but no data were presented). Score “High risk” if there is no report of characteristics in text or tables or if there are differences between control and intervention providers. Note that in some cases imbalance in patient characteristics may be due to recruitment bias whereby the provider was responsible for recruiting patients into the trial.

Were incomplete outcome data adequately addressed?

Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the intervention and control groups or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “High risk” if missing outcome data was likely to bias the results. Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

Was knowledge of the allocated interventions adequately prevented during the study?

Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “High risk” if the outcomes were not assessed blindly. Score “Unclear risk” if not specified in the paper.

Was the study adequately protected against contamination?

Score “Low risk” if allocation was by community, institution or practice and it is unlikely that the control group received the intervention. Score “High risk” if it is likely that the control group received the intervention (e.g. if patients rather than professionals were randomised). Score “Unclear risk” if professionals were allocated within a clinic or practice and it is possible that communication between intervention and control professionals could have occurred (e.g. physicians within practices were allocated to intervention or control)

Was the study free from selective outcome reporting?

Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “High risk” if some important outcomes are subsequently omitted from the results. Score “Unclear risk” if not specified in the paper.

Was the study free from other risks of bias?

Score “Low risk” if there is no evidence of other risk of biases.

Appendix G. Risk of Bias for observational studies: Newcastle Ottawa Scale (NOS) – Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average _____ (describe) in the community ★
- b) somewhat representative of the average _____ in the community ★
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort ★
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (eg surgical records) ★
- b) structured interview ★
- c) written self-report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes ★
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for _____ (select the most important factor) ★
- b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blind assessment ★
- b) record linkage ★
- c) self report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest) ★
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for ★
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ★
- c) follow up rate < ____ % (select an adequate %) and no description of those lost
- d) no statement

Appendix H. Risk of Bias for observational studies: Newcastle Ottawa Scale (NOS) – Case-Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

- a) yes, with independent validation ★
- b) yes, eg record linkage or based on self-reports
- c) no description

2) Representativeness of the cases

- a) consecutive or obviously representative series of cases ★
- b) potential for selection biases or not stated

3) Selection of Controls

- a) community controls ★
- b) hospital controls
- c) no description

4) Definition of Controls

- a) no history of disease (endpoint) ★
- b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

- a) study controls for _____ (Select the most important factor.) ★
- b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

- a) secure record (eg surgical records) ★
- b) structured interview where blind to case/control status ★
- c) interview not blinded to case/control status
- d) written self-report or medical record only
- e) no description

2) Same method of ascertainment for cases and controls

- a) yes ★
- b) no

3) Non-Response rate

- a) same rate for both groups ★
- b) non respondents described
- c) rate different and no designation

Appendix I. EPOC risk of bias for Interrupted Time Series (ITS) studies

1. Was the intervention independent of other changes?

Score “Low risk” if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. Score “High risk” if reported that intervention was not independent of other changes in time.

2. Was the shape of the intervention effect pre-specified?

Score “Low risk” if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. Score “High risk” if it is clear that the condition above is not met.

3. Was the intervention unlikely to affect data collection?

Score “Low risk” if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score “High risk” if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).

4. Was knowledge of the allocated interventions adequately prevented during the study?

Score “Low risk” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “High risk” if the outcomes were not assessed blindly. Score “Unclear risk” if not specified in the paper.

5. Were incomplete outcome data adequately addressed?

Score “Low risk” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “High risk” if missing outcome data was likely to bias the results. Score “Unclear risk” if not specified in the paper (Do not assume 100% follow up unless stated explicitly).

6. Was the study free from selective outcome reporting?

Score “Low risk” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “High risk” if some important outcomes are subsequently omitted from the results. Score “Unclear risk” if not specified in the paper.

7. Was the study free from other risks of bias?

Score “Low risk” if there is no evidence of other risk of biases. e.g. should consider if seasonality is an issue (i.e. if January to June comprises the pre-intervention period and July to December the post, could the “seasons’ have caused a spurious effect).

Appendix J. Search strategy for Key Question 2: Patient preferences and values

Database: Embase Classic+Embase <1947 to 2016 December 22>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

- 1 exp Gastroesophageal Reflux/ (81152)
- 2 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (57298)
- 3 GERD.tw,kw. (20842)
- 4 GORD.tw,kw. (2028)
- 5 SEGR.tw,kw. (15)
- 6 (gastric adj2 regurgitat*).tw,kw. (491)
- 7 or/1-6 [GERD] (95636)
- 8 Esophageal Neoplasms/ (57546)
- 9 exp Esophagus/ and exp Neoplasms/ (41049)
- 10 ((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. (106984)
- 11 Barrett Esophagus/ (22094)
- 12 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome?)).tw,kw. (21731)
- 13 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw. (228507)
- 14 or/8-13 [ESOPHAGEAL CANCER] (367024)
- 15 7 and 14 [GERD AND ESOPHAGEAL CANCER] (13618)
- 16 exp Infant/ not (exp Adult/ and exp Infant/) (1668414)
- 17 exp Child/ not (exp Adult/ and exp Child/) (3166639)
- 18 15 not (16 or 17) [CHILD-ONLY REMOVED] (13152)
- 19 exp Animals/ not (exp Animals/ and Humans/) (16540312)
- 20 18 not 19 [ANIMAL-ONLY REMOVED] (9687)
- 21 (comment or editorial or news).pt. (1759554)
- 22 (letter not (letter and randomized controlled trial)).pt. (1975451)
- 23 20 not (21 or 22) [OPINION PIECES REMOVED] (9147)
- 24 exp Gastroesophageal Reflux/px (408)
- 25 Esophageal Neoplasms/px (212)
- 26 Barrett Esophagus/px (38)
- 27 Mass Screening/px (2235)
- 28 Early Detection of Cancer/px (952)
- 29 Diagnostic Tests, Routine/px (92)
- 30 Endoscopy/px (75)
- 31 Endoscopy, Gastrointestinal/px (79)
- 32 Esophagoscopy/px (19)
- 33 Gastroscopy/px (66)
- 34 or/24-33 [PSYCHOLOGICAL ASPECTS RE: DISEASE AND SCREENING TECHNIQUES] (3989)
- 35 exp Adaptation, Psychological/ (175473)
- 36 Attitude/ (104240)
- 37 Attitude to Death/ (25701)
- 38 exp Attitude to Health/ (477262)
- 39 Choice Behavior/ (218838)
- 40 Consumer Advocacy/ (6482)
- 41 *Consumer Behavior/ (10008)
- 42 exp Consumer Participation/ (101600)
- 43 Cooperative Behavior/ (79087)
- 44 Decision Making/ (304577)
- 45 Focus Groups/ (217220)
- 46 Health Care Surveys/ (38372)
- 47 Health Services Accessibility/ (196643)
- 48 Interviews as Topic/ (200131)
- 49 Life Change Events/ (47137)
- 50 Narration/ (19635)
- 51 Patient Acceptance of Health Care/ (90941)
- 52 Patient Advocacy/ (44936)
- 53 exp Patient-Centered Care/ (706139)
- 54 exp Patient Education as Topic/ (184289)
- 55 Patient Participation/ (45671)
- 56 Patient Preference/ (17740)

57 Patient Satisfaction/ (184113)
58 exp Patients/px (15246)
59 Personal Autonomy/ (27647)
60 **Power (Psychology)"/ (67392)
61 Questionnaires/ (848656)
62 Quality of Life/px (20574)
63 exp Self Concept/ (309160)
64 Self Efficacy/ (63336)
65 exp Self-Help Groups/ (23875)
66 Social Values/ (98553)
67 ((accept* or anxiet* or anxious* or attitud* or consider* or choice? or choos* or chose? or concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or satisf* or unsatisf* or value? or valuing or view* or worrie? or worry*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).tw,kf. (1609291)
68 (advoca* adj3 (client? or consumer? or patient?)).tw,kf. (11123)
69 ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf. (2884)
70 (autonom* adj3 (personal* or self)).tw,kf. (4306)
71 (choice? adj1 (discrete or experiment*)).tw,kf. (5032)
72 ((client? or consumer? or patient?) adj (centered or centred or focus*)).tw,kf. (42918)
73 ((client? or consumer? or patient? or personal) adj narrati*).tw,kf. (1865)
74 empower*.tw,kf. (41212)
75 (focus group? or interview* or questionnaire? or survey*).tw,kf. (2441834)
76 (freedom? or libert*).tw,kf. (91872)
77 gamb1*.tw,kf. (18696)
78 ((health or death) adj3 (anxiet* or anxious* or attitud* or concern* or fear* or feel? or feeling* or felt or perception* or perspective? or prefer* or view* or worrie? or worry*)).tw,kf. (142594)
79 health utilit*.tw,kf. (4086)
80 informed choice?.tw,kf. (4662)
81 (life adj3 (event? or experience?)).tw,kf. (57703)
82 (multi?attribute or multi?criteria).tw,kf. (1854)
83 (preference? adj1 (elicit* or scor* or stated)).tw,kf. (2957)
84 prospect theor*.tw,kf. (464)
85 (self adj2 (conceiv* or concept* or percepti* or perceiv*)).tw,kf. (41335)
86 (self adj (determin* or efficac* or help or manag* or support*)).tw,kf. (96180)
87 (social* adj1 valu*).tw,kf. (3619)
88 trade?off?.tw,kf. (10709)
89 (willing* adj2 pay*).tw,kf. (11145)
90 or/35-89 [COMBINED MeSH & TEXT WORDS FOR PATIENT PREFERENCES & VALUES] (6179901)
91 exp Communication/ (1126396)
92 ((time\$2 or timeliness) adj2 (communica* or info*)).tw,kf. (14470)
93 (miscommunicat* or mis-communicat*).tw,kf. (1496)
94 (misunderstand* or mis-understand*).tw,kf. (10770)
95 (misinform* or mis-inform*).tw,kf. (4760)
96 ((involv* or participat*) adj3 (client? or consumer? or patient?)).tw,kf. (189474)
97 exp Informed Consent/ (131530)
98 (informed adj (choice* or choos* or consent* or decision*)).tw,kf. (106163)
99 (choice? adj2 behavio?r*).tw,kf. (4971)
100 ((client? or consumer? or patient? or personal) adj3 consent*).tw,kf. (33377)
101 ((make or making or makes or made or shar* or support*) adj2 (choice? or choos* or decision*)).tw,kf. (317113)
102 Patient Reported Outcome Measures/ (57)
103 patient reported outcome?.tw,kf. (23580)
104 (PROM or PROMs or ePREM or ePREMs).tw,kf. (6155)
105 or/91-104 [PATIENT COMMUNICATION / MISCOMMUNICATION / CONSENT / SUPPORT] (1792154)
106 90 or 105 (7215724)
107 34 or 106 [ALL PATIENT PREFERENCES & VALUES SETS] (7216199)
108 23 and 107 [GERD/ESOPHAGEAL CANCER - PATIENT PREFERENCES & VALUES] (1529)
109 108 use ppez [MEDLINE RECORDS] (691)
110 gastroesophageal reflux/ (73427)
111 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (57298)
112 GERD.tw,kw. (20842)
113 GORD.tw,kw. (2028)
114 SEGR.tw,kw. (15)
115 (gastric adj2 regurgitat*).tw,kw. (491)
116 or/110-115 (89049)
117 exp esophagus tumor/ (70160)

118 exp esophagus/ and exp neoplasm/ (41049)
119 ((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. (106984)
120 Barrett Esophagus/ (22094)
121 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplas* or syndrome?)).tw,kw. (21731)
122 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kw. (228507)
123 or/117-122 (369397)
124 116 and 123 [GERD AND ESOPHAGEAL CANCER] (12695)
125 exp juvenile/ not (exp juvenile/ and exp adult/) (2227591)
126 exp Infant/ not (exp Adult/ and exp Infant/) (1668414)
127 exp Child/ not (exp Adult/ and exp Child/) (3166639)
128 or/125-127 (3878944)
129 124 not 128 [CHILD, 17 AND UNDER, REMOVED] (12234)
130 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46667050)
131 exp human/ or exp human experimentation/ or exp human experiment/ (36658748)
132 130 not 131 (10010048)
133 129 not 132 [ANIMAL-ONLY REMOVED] (11918)
134 editorial.pt. (984477)
135 letter.pt. not (letter.pt. and randomized controlled trial/) (1970170)
136 133 not (134 or 135) [OPINION PIECES REMOVED] (11291)
137 adaptive behavior/ (143300)
138 attitude/ (104240)
139 attitude to death/ (25701)
140 attitude to disability/ (284)
141 attitude to health/ (177664)
142 attitude to illness/ (4223)
143 attitude to life/ (565)
144 consumer advocacy/ (6482)
145 consumer attitude/ (2724)
146 cooperation/ (41693)
147 decision making/ (304577)
148 health care survey/ (43078)
149 exp interview/ (284456)
150 life event/ (27486)
151 patient advocacy/ (44936)
152 exp patient attitude/ (323062)
153 patient decision making/ (8138)
154 exp patient education/ (184289)
155 personal autonomy/ (27647)
156 psychological aspect/ (478328)
157 exp questionnaire/ (1501270)
158 exp self concept/ (309160)
159 self help/ (13450)
160 exp social psychology/ (943571)
161 ((accept* or anxiet* or anxious* or attitud* or consider* or choice? or choos* or chose? or concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or satisf* or unsatisf* or value? or valuing or view* or worrie? or worry*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stakeholder* or user? or wom#n)).tw,kf. (1609291)
162 (advoca* adj3 (client? or consumer? or patient?)).tw,kf. (11123)
163 ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf. (2884)
164 (autonom* adj3 (personal* or self)).tw,kf. (4306)
165 (choice? adj1 (discrete or experiment*)).tw,kf. (5032)
166 ((client? or consumer? or patient?) adj (centered or centred or focus*)).tw,kf. (42918)
167 ((client? or consumer? or patient? or personal) adj narrati*).tw,kf. (1865)
168 empower*.tw,kf. (41212)
169 (focus group? or interview* or questionnaire? or survey*).tw,kf. (2441834)
170 (freedom? or libert*).tw,kf. (91872)
171 gambli*.tw,kf. (18696)
172 ((health or death) adj3 (anxiet* or anxious* or attitud* or concern* or fear* or feel? or feeling* or felt or perception* or perspective? or prefer* or view* or worrie? or worry*)).tw,kf. (142594)
173 health utilit*.tw,kf. (4086)
174 informed choice?.tw,kf. (4662)
175 (life adj3 (event? or experience?)).tw,kf. (57703)
176 (multi?attribute or multi?criteria).tw,kf. (1854)
177 (preference? adj1 (elicit* or scor* or stated)).tw,kf. (2957)
178 prospect theor*.tw,kf. (464)

179 (self adj2 (conceiv* or concept* or percepti* or perceiv*).tw,kf. (41335)
180 (self adj (determin* or efficac* or help or manag* or support*).tw,kf. (96180)
181 (social* adj1 valu*).tw,kf. (3619)
182 trade?off?.tw,kf. (10709)
183 (willing* adj2 pay*).tw,kf. (11145)
184 or/137-183 [Combined MeSH & text words for patient preferences & values] (6339037)
185 communication/ (223659)
186 exp verbal communication/ (346309)
187 ((time\$2 or timeliness) adj2 (communica* or info*).tw,kf. (14470)
188 (miscommunicat* or mis-communicat*).tw,kf. (1496)
189 (misunderstand* or mis-understand*).tw,kf. (10770)
190 (misinform* or mis-inform*).tw,kf. (4760)
191 ((involv* or participat*) adj3 (client? or consumer? or patient?)).tw,kf. (189474)
192 informed consent/ (126689)
193 (informed adj (choic* or choos* or consent* or decision*).tw,kf. (106163)
194 (choic? adj2 behavio?r*).tw,kf. (4971)
195 ((client? or consumer? or patient? or personal) adj3 consent*).tw,kf. (33377)
196 ((make or making or makes or made or shar* or support*) adj2 (choic? or choos* or decision*).tw,kf. (317113)
197 patient reported outcome?.tw,kf. (23580)
198 (PROM or PROMs or ePREM or ePREMs).tw,kf. (6155)
199 or/185-198 [Additional patient preference terms] (1242082)
200 184 or 199 [ALL PATIENT PREFERENCES & VALUES SETS] (7011853)
201 136 and 200 [GERD/ESOPHAGEAL CANCER - PATIENT PREFERENCES & VALUES] (2127)
202 201 use emczd [EMBASE RECORDS] (1260)
203 109 or 202 [BOTH DATABASES] (1951)
204 remove duplicates from 203 (1373) [TOTAL UNIQUE RECORDS]
205 204 use ppez [MEDLINE UNIQUE RECORDS] (599)
206 204 use emczd [EMBASE UNIQUE RECORDS] (774)

Cochrane Library

Search Name: CTFPHC - Esophageal Cancer - GERD - Patient Preferences - No Screening Filters
Date Run: 23/12/16 18:37:37.513
Description: CTFPHC (OHRI) - 2016 Dec 23

ID	Search	Hits
#1	[mh "Gastroesophageal Reflux"]	1628
#2	((esophageal or gastric* or (gastro next esophageal) or (gastro next oesophageal) or supraesophageal or (supra next esophageal) or supraoesophageal or (supra next oesophageal)) near/2 reflux*):ti,ab,kw	996
#3	GERD:ti,ab,kw	840
#4	GORD:ti,ab,kw	133
#5	SEGR:ti,ab,kw	0
#6	(gastric near/2 regurgitat*):ti,ab,kw	48
#7	{or #1-#6}	2481
#8	[mh "Esophageal Neoplasms"]	1183
#9	[mh Esophagus] and [mh Neoplasms]	239
#10	((esophag* or oesophag* or (pharynx next esophag*)) near/3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or (adeno next carcinoma*) or carcinosarcoma* or (carcino next sarcoma*)):ti,ab,kw	2702
#11	[mh "Barrett Esophagus"]	240
#12	(Barrett* near/1 (esophag* or oesophag* or epitheli* or metaplas* or syndrome*)):ti,ab,kw	351
#13	(dysplasia* or dysplastic* or precancer* or (pre next cancer*) or premalignan* or (pre next malignan*)):ti,ab,kw	2754
#14	{or #8-#13}	5408
#15	#7 and #14	102
#16	[mh Infant] not ([mh Adult] and [mh Infant])	14659
#17	[mh Child] not ([mh Adult] and [mh Infant])	203
#18	[mh Juvenile] not ([mh Adult] and [mh Infant])	0
#19	#15 not (#16 or #17 or #18)	100
#20	[mh "Gastroesophageal Reflux"/PX]	33
#21	[mh "Esophageal Neoplasms"/PX]	18
#22	[mh "Barrett Esophagus"/PX]	1
#23	[mh "Mass Screening"/PX]	193
#24	[mh "Early Detection of Cancer"/PX]	68
#25	[mh "Diagnostic Tests, Routine"/PX]	4
#26	[mh Endoscopy/PX]	178

#27	[mh "Endoscopy, Gastrointestinal"/PX]	89
#28	[mh Esophagoscopy/PX]	0
#29	[mh Gastroscopy/PX]	10
#30	{or #20-#29}	458
#31	[mh "Adaptation, Psychological"]	4600
#32	[mh ^Attitude]	940
#33	[mh "Attitude to Death"]	137
#34	[mh "Attitude to Health"]	30538
#35	[mh "Choice Behavior"]	1129
#36	[mh "Consumer Advocacy"]	14
#37	[mh "Consumer Behavior" [mj]]	545
#38	[mh "Consumer Participation"]	1316
#39	[mh "Cooperative Behavior"]	884
#40	[mh ^"Decision Making"]	2027
#41	[mh "Focus Groups"]	401
#42	[mh "Health Care Surveys"]	364
#43	[mh ^"Health Services Accessibility"]	700
#44	[mh "Interviews as Topic"]	1571
#45	[mh "Life Change Events"]	444
#46	[mh Narration]	138
#47	[mh ^"Patient Acceptance of Health Care"]	2409
#48	[mh "Patient Advocacy"]	75
#49	[mh "Patient-Centered Care"]	495
#50	[mh "Patient Education as Topic"]	7775
#51	[mh "Patient Participation"]	1068
#52	[mh "Patient Preference"]	535
#53	[mh "Patient Satisfaction"]	10531
#54	[mh Patients/PX]	467
#55	[mh "Personal Autonomy"]	157
#56	[mh "Power (Psychology)" [mj]]	217
#57	[mh "Surveys and Questionnaires"]	46567
#58	[mh "Quality of Life"/PX]	1586
#59	[mh "Self Concept"]	5509
#60	[mh "Self Efficacy"]	2144
#61	[mh "Self-Help Groups"]	741
#62	[mh "Social Values"]	157
#63	((accept* or anxiet* or anxious* or attitud* or consider* or choice* or choos* or chose* or concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or opinion* or participat* or perceiv* or percepti* or perspective* or prefer* or respons* or satisf* or unsatisf* or value* or valuing or view* or worrie* or worry*) near/3 (citizen* or client* or consumer* or female* or male* or men or patient* or public or stake*holder* or user* or woman or women)):ti,ab,kw	94200
#64	(advoca* near/3 (client* or consumer* or patient*)):ti,ab,kw	252
#65	((analys* or valuation* or value* or valuing) near/3 (conjoint or contingent)):ti,ab,kw	80
#66	(autonom* near/3 (personal* or self)):ti,ab,kw	266
#67	(choice* near/1 (discrete or experiment*)):ti,ab,kw	98
#68	((client* or consumer* or patient*) next (centered or centred or focus*)):ti,ab,kw	1599
#69	((client* or consumer* or patient* or personal) next narrati*):ti,ab,kw	28
#70	empower*:ti,ab,kw	1044
#71	("focus group" or "focus groups" or interview* or questionnaire* or survey*):ti,ab,kw	78624
#72	(freedom* or libert*):ti,ab,kw	2129
#73	gamb*:ti,ab,kw	552
#74	((health or death) near/3 (anxiet* or anxious* or attitud* or concern* or fear* or feel or feels or feeling* or felt or perception* or perspective* or prefer* or view* or worrie* or worry*)):ti,ab,kw	12600
#75	(health next utilit*):ti,ab,kw	294
#76	(informed next choice*):ti,ab,kw	192
#77	(life near/3 (event* or experience*)):ti,ab,kw	1560
#78	(multi*attribute or multi*criteria):ti,ab,kw	27
#79	(preference* near/1 (elicit* or scor* or stated)):ti,ab,kw	138
#80	(prospect next theor*):ti,ab,kw	27
#81	(self near/2 (conceiv* or concept* or percepti* or perceiv*)):ti,ab,kw	5154
#82	(self next (determin* or efficac* or help or manag* or support*)):ti,ab,kw	9945
#83	(social* near/1 valu*):ti,ab,kw	216
#84	trade*off*:ti,ab,kw	132
#85	(willing* near/2 pay*):ti,ab,kw	640
#86	[mh Communication]	12012
#87	(time* near/2 (communica* or info*)):ti,ab,kw	316
#88	mis*communicat*:ti,ab,kw	20

#89	mis*understand*:ti,ab,kw	110
#90	mis*inform*:ti,ab,kw	61
#91	((involv* or participat*) near/3 (client* or consumer* or patient*)):ti,ab,kw	13061
#92	[mh "Informed Consent"]	612
#93	(informed next (choice* or choos* or consent* or decision*)):ti,ab,kw	7310
#94	(choice* near/2 behavio*):ti,ab,kw	1159
#95	((client* or consumer* or patient* or personal) near/3 consent*):ti,ab,kw	3463
#96	((make or making or makes or made or shar* or support*) near/2 (choice* or choos* or decision*)):ti,ab,kw	10260
#97	[mh "Patient Reported Outcome Measures"]	0
#98	("patient reported" next outcome*):ti,ab,kw	1967
#99	(PROM or PROMS or ePREM or ePREMs):ti,ab,kw	311
#100	{or #31-#99}	218619
#101	#30 or #100	218649
#102	#19 and #101	37

DSR – 3
CENTRAL – 27
NHS EED - 7

Appendix K. CASP Qualitative Checklist

Screening Questions

1. **Was there a clear statement of the aims of the research?** Yes Can't tell No

HINT: Consider

- What was the goal of the research?
- Why it was thought important?
- Its relevance

2. **Is a qualitative methodology appropriate?** Yes Can't tell No

HINT: Consider

- If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal?

Is it worth continuing?

3. **Was the research design appropriate to address the aims of the research?**

Yes Can't tell No

HINT: Consider

- If the researcher has justified the research design (e.g. have they discussed how they decided which method to use)?

4. **Was the recruitment strategy appropriate to the aims of the research?** Yes Can't tell No

HINT: Consider

- If the researcher has explained how the participants were selected
- If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
- If there are any discussions around recruitment (e.g. why some people chose not to take part)

5. **Was the data collected in a way that addressed the research issue?** Yes Can't tell No

HINT: Consider

- If the setting for data collection was justified
- If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
- If the researcher has justified the methods chosen
- If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews were conducted, or did they use a topic guide)?
- If methods were modified during the study. If so, has the researcher explained how and why?
- If the form of data is clear (e.g. tape recordings, video material, notes etc)
- If the researcher has discussed saturation of data

6. **Has the relationship between researcher and participants been adequately considered?**

Yes Can't tell No

HINT: Consider

- If the researcher critically examined their own role, potential bias and influence during (a) Formulation of the research questions (b) Data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

7. Have ethical issues been taken into consideration? Yes Can't tell No

HINT: Consider

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

8. Was the data analysis sufficiently rigorous? Yes Can't tell No

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data?
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
- To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

9. Is there a clear statement of findings? Yes Can't tell No

HINT: Consider

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researchers arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

10. How valuable is the research?

HINT: Consider

- If the researcher discusses the contribution the study makes to existing knowledge or understanding e.g. do they consider the findings in relation to current practice or policy?, or relevant research-based literature?
- If they identify new areas where research is necessary
- If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used