Evidence-based Practice Center Systematic Review Protocol

Project Title: *Management of Colonic Diverticulitis*

I. Background

Colonic diverticulitis is caused by inflammation of abnormal outpouchings (diverticula) in the wall of the large intestine. The precursor to diverticulitis is diverticulosis, in which the diverticula are not inflamed. They typically are asymptomatic, but may result in pain, bloating, or generally mild gastrointestinal symptoms. About 5 to 10 percent of patients with diverticulosis develop symptomatic diverticulitis,[1] and the number of emergency department admissions for diverticulitis has been increasing over time.[2] About 60% of people over the age of 60 have diverticulosis; up to 25% of these people are likely to progress to diverticulitis.[3, 4] Recent data reveal that 10 percent of Americans younger than 40 years have diverticulosis and are thus at risk for developing acute diverticulitis.[5] Due to high hospitalization rates and related costs, in the setting of potentially feasible outpatient management, diverticulitis has been prioritized as a measure to compare and reduce variability across national emergency department admission rates.[6]

Symptoms of diverticulitis typically involve acute or subacute lower abdominal pain, often associated with nausea, diarrhea, or constipation. While early studies suggested that diverticulitis is a recurrent disease of a progressive nature, more recent studies in the era of improved medical treatment and more reliable diagnostic imaging suggest the natural history is more benign.[7, 8] The high accuracy of computed tomography (CT) scanning[9] has made it the mainstay for diagnosis of suspected diverticulitis. The prognostic value of CT scanning has had a great impact on accurate diagnosis and staging, which has affected clinical management.[10, 11] However, its ubiquitous use has raised concerns about diagnostic errors (whether false positive or false negative) and the potential impact of incidental findings on CTs conducted to rule out or assess diverticulitis (e.g., abnormal liver masses that may need invasive or costly workups).

Acute episodes of diverticulitis may be complicated or uncomplicated. Complications are mostly caused by small or large perforations to the diverticula, which may introduce gut bacteria into the peritoneal space. Complications include abscesses, peritonitis, fistulas, and strictures; complications occur in about 15 to 20 percent of cases of acute diverticulitis. Several schema to classify diverticulitis severity have been published,[12] from the earliest one by Hughes in 1963,[13] to one recently proposed by the European Association for Endoscopic Surgery.[14] Most widely used is the Hinchey Classification,[15] which has been modified to include mild clinical disease,[16] and further updated to reflect CT findings to help not just with diagnosis but also with prognosis.[10, 11] Multiple other classification schemes exist that mostly stage severity, complications, and relapses,[14, 17, 18] or CT findings.[11, 19]

Traditional management for patients with uncomplicated diverticulitis includes hospitalization for bowel rest, antibiotics, and intravenous (IV) fluids. Management of complicated diverticulitis may require more intensive and invasive interventions, including open or laparoscopic surgeries or interventional radiology procedures to bypass or remove the affected portion of bowel or to

drain or cleanse the peritoneal space. In recent years, several controversies have emerged with regards to the optimal management of acute diverticulitis.[20] Recent narrative reviews highlighted where current common practices in the management of acute diverticulitis, including medical, surgical, and interventional radiological, may not be supported by the evidence for all patients, including universal hospitalization, use of IV antibiotics, and colectomy and other aggressive surgical procedures for complicated episodes.[20, 21] For example, a recent randomized controlled trial suggested there was no difference in treatment failure between admission and outpatient management with considerable cost savings in the latter group.[22] The duration of antibiotic treatment[23] and the need for antibiotics[24, 25] have been questioned. A recent systematic review of current strategies for uncomplicated diverticulitis revealed unproven differences in outcomes between observational management and antibiotic therapy and between oral and IV antibiotics.[26]

Due to unfavorable mortality and complication rates for emergent surgery for acute complicated diverticulitis, physicians have opted to delay definitive surgical management by employing antibiotics and interventional radiology procedures, such as percutaneous drainage of abscess in appropriate patients; but the supporting evidence for this approach is unclear.

Patients with a diverticulitis complicated by an abscess have traditionally been offered an interval (non-emergency, elective) colectomy after treatment with antibiotics and possible percutaneous drainage. The rationale for subsequent surgery was to prevent future complications, but recent studies have found that nonsurgical, continued medical treatment of diverticulitis is safe, with low rates of subsequent surgery.[27] More current literature has increasingly revealed that diverticulitis is not a progressive disease as once thought, and that increasing number of episodes do not lead to more complications or the need for urgent operative management. Indeed, studies have found that the greatest risk of free perforation and peritonitis is during the first episode of the disease.[28] Moreover, the risk of recurrence is likely much lower than previously thought.[29] Accordingly, rates of interval colectomy have been declining since the early 2000s in some areas of North America.[30] with a corresponding increase in interventional radiology approaches, such as percutaneous abscess drainage via ultrasonography or CT image-guided catheter placements. Initially reserved for the sickest, highest-risk surgical patients, drainage and antibiotic treatment is now used as definitive treatment to avoid surgery and allow shorter hospital stay and faster recovery.[31, 32]

The natural course of diverticulitis was once thought to be more aggressive in younger patients (<50 years) than it is currently believed to be[33, 34]; thus it is currently less common to electively operate on younger patients with a history of diverticulitis. In contrast, a lower threshold for both elective and emergency surgical intervention continues to be recommended for immunocompromised patients, such as people with organ transplants, receiving chemotherapy, or with chronic kidney disease.[35, 36]

Strategies to reduce (or eliminate) diverticulitis recurrence have evolved. Despite very low quality of evidence,[37, 38] guidelines recommend high-fiber diets, but no longer recommend avoiding seeds, nuts, and popcorn. Various pharmacologic treatments are used in clinical practice, although uncertainty remains. For example, the 2015 American Gastroenterological Association guideline recommended against using mesalamine (5-aminosalicylic acid or 5-ASA), an anti-inflammatory agent that is effective for ulcerative colitis;[38] but a more recent systematic review concluded that mesalamine may reduce recurrences in symptomatic uncomplicated diverticular disease.[39]

There remain unanswered questions regarding the potential adverse consequences of CT imaging (related to false positive tests that may lead to further invasive testing and surgery) to diagnose uncomplicated and complicated diverticulitis. The evidence regarding this potential harm has not been summarized to date.

Another area of controversy includes the appropriateness of performing colonoscopy following a resolved episode of diverticulitis to detect occult colonic malignancy.[40] CT features of acute diverticulitis may mimic colon cancer;[41] thus professional societies have recommended followup colonoscopy to exclude colon cancer after an episode of acute diverticulitis.[42] However, the prevalence of colorectal cancer in this setting has been found to be low for patients with uncomplicated diverticulitis,[43] leading some authors to question the need for routine colon evaluation for these patients. The value of CT (or virtual) colonography, noninvasive imaging of the interior lumen of the colon, for colon evaluation in this setting requires more study. Although it may be associated with less pain and more patient tolerance, its diagnostic accuracy is uncertain.[44]

Purpose of the Review

The American College of Physicians (ACP) nominated the topic of management of acute diverticulitis to the Agency for Healthcare Research and Quality for systematic review. [45, 46] The ACP develops guidelines based on the needs of its members and the internal medicine community.[47] The scope of the current systematic review was developed to support the ACP in its effort to create a new clinical practice guideline that will address diagnosis and staging of acute diverticulitis, nonsurgical treatment of acute diverticulitis, colorectal cancer screening in people with a history of diverticulitis, and interventions to prevent recurrence of acute diverticulitis.

Specifically, (1) the systematic review will summarize existing systematic reviews on the test accuracy of CT imaging for diagnosis and staging of acute diverticulitis and conduct a *de novo* review of harms related to false positive, false negative, and incidental findings on CT imaging for suspected acute diverticulitis; (2) it will address effectiveness, comparative effectiveness, and harms of hospitalization for acute uncomplicated diverticulitis, antibiotics use for acute complicated or uncomplicated diverticulitis, and interventional radiology techniques for acute complicated diverticulitis; (3) it will review the benefits and harms of colonoscopy in people with a history of diverticulitis; and (4) it will evaluate pharmacologic, nonpharmacologic, and elective surgical interventions to prevent recurrent diverticulitis. Of note, this review will not evaluate the need for, or the choice of, surgery for the patient with acute diverticulitis.

The intended audience includes guideline developers, clinicians and other providers of care for patients with diverticulitis, healthcare policy makers, and patients.

II. Key Questions

KQ 1: In CT imaging for the diagnosis or staging of acute diverticulitis,

KQ 1a. What is the test accuracy of CT imaging for the diagnosis or staging of acute diverticulitis?

KQ 1b. What are the effects of CT imaging on clinical outcomes and changes in clinical management?

KQ 1c. What are the downstream outcomes related to false positive or false negative CT readings of acute uncomplicated or complicated diverticulitis

KQ 1d. For patients presenting with acute abdominal pain, with the possibility of acute diverticulitis, what are the downstream outcomes related to incidental findings (e.g., liver mass)

- Does the accuracy or do the effects vary by patient characteristics, presentation of illness, or other factors?

KQ 2: What are the benefits and harms of various treatment options for the treatment of acute diverticulitis?

KQ 2a. For patients with acute uncomplicated diverticulitis, what are the effectiveness and harms of hospitalization versus outpatient management of the acute episode?

- Do the effects and harms vary by patient characteristics, presentation or course of illness, or other factors?

KQ 2b. For patients with acute uncomplicated or complicated diverticulitis, what are the effects, comparative effects, and harms of antibiotics?

- Do the effects and harms vary between patients with complicated or uncomplicated diverticulitis?
- Do the (comparative) effects and harms vary by route of administration of antibiotics, type of antibiotic, and duration of course of antibiotics?
- Do the (comparative) effects and harms vary by patient characteristics, presentation or course of illness, or other factors?

KQ 2c. For patients with acute complicated diverticulitis, what are the effects and harms of interventional radiology procedures compared with conservative management?

- Do the effects and harms vary by patient characteristics, presentation or course of illness, or other factors?

KQ 3: What are the benefits and harms of colonoscopy (or other colon imaging test) following an episode of acute diverticulitis?

KQ 3a. What is the incidence of malignant and premalignant colon tumors found by colonoscopy, and what is the incidence of colon cancer mortality among patients undergoing screening?

KQ 3b. What are the procedure-related and other harms of colonoscopy or CT colonography?

KQ 3c. What is the frequency of inadequate imaging due to intolerance or technical feasibility?

- Do the benefits and harms vary by patient characteristics, course of illness, or other factors?

KQ 4: What are the effects, comparative effects, and harms of pharmacological interventions (e.g., mesalamine), non-pharmacological interventions (e.g., medical nutrition therapy), and elective surgery to prevent recurrent diverticulitis?

- Do the (comparative) effects and harms vary by patient characteristics, course of illness, or other factors?

Study Eligibility Criteria for KQ 1 (CT imaging)

Population(s):

- KQ 1 (all): Adults with suspected or known diagnosis of acute colonic diverticulitis
  - Suspected diagnosis for diagnosis of acute diverticulitis
  - Known diagnosis for staging of disease
  - Exclude: Non-colonic diverticulitis (except for KQ 1d)
- KQ 1d: Adults with acute abdominal pain who receive an abdominal CT

Intervention:

- CT (computed tomography) scan
  - With or without IV (intravenous), oral, or rectal contrast

Comparators:

- No CT scanning (as an explicit comparator)
- MRI (magnetic resonance imaging)
- Ultrasonography
- Other diagnostic interventions
- No comparator (single group studies)

Outcomes:

- KQ 1a: Diagnostic accuracy (from existing systematic reviews only)
  - Acute diverticulitis vs. other condition
  - Complicated vs. uncomplicated diverticulitis
  - For staging of severity
- KQ 1b: Clinical outcomes
  - Short-term (≤1 month)
    - Time to resolution of acute diverticulitis
    - Length of hospital stay
    - Conversion to complicated diverticulitis
    - Diverticulitis-related morbidities (e.g., abscess formation) and mortality
    - Change in management (treatment decisions)
  - Medium- (>1 to <12 mo) to long-term (≥1 year)
    - Recurrent diverticulitis
    - Future episode of complicated diverticulitis
    - Diverticulitis-related morbidities (e.g., strictures) and mortality
- KQ 1c: Harms
  - Harms of over-treatment (due to false positive findings; e.g., surgery, stress)

    - Harms of under-treatment (due to false negative findings; e.g., peritonitis, unnecessary surgery for other condition)
- KQ 1d: Incidental findings
    - Sequelae related to incidental findings (e.g., unnecessary liver biopsy)

Modifiers/Subgroups of interest

- Patient characteristics (e.g., prior history of diverticulitis, age)
- Presentation of illness (e.g., specific signs or symptoms, such as large volume ascites)
- Other factors (e.g., complicated or uncomplicated diverticulitis, hospital setting)

Timing

- Any

Setting

- Inpatient, emergency department (or equivalent), outpatient

Design

- KQ 1a: For test accuracy:
    - Existing systematic reviews
- KQ 1b, 1c, 1d: For clinical outcomes and harms:
    - Prospective
    - Retrospective only if unbiased sampling (inclusion criteria based on pre-imaging criteria only)
    - N≥20 receiving CT*
    - Publication since 1990†

Study Eligibility Criteria for KQ 2 (Treatment of acute diverticulitis)

Population(s):

- Adults with acute complicated or uncomplicated diverticulitis, whether first or recurrent episode
    - KQ 2a: Intervention = hospitalization: uncomplicated diverticulitis
    - KQ 2b: Intervention = antibiotics: uncomplicated or complicated diverticulitis
    - KQ 2c: Intervention = interventional radiology: complicated diverticulitis (e.g., abscess)
- Exclude: Complicated diverticulosis, without diverticulitis (e.g., hemorrhagic diverticulosis)
- Exclude: Symptomatic uncomplicated diverticular disease (SUDD)
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions versus Comparators:

- Hospitalization versus No hospitalization (for patients not requiring surgery)

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* The minimum sample size may be adjusted upward depending on the number of available studies.

† Older studies are of little relevance to contemporary practice given changes in diagnostic test modalities (e.g., improvement in CT speed, increased slice count, radiation dose and image quality; use of ultrasonography and barium enemas). CT began to be used commonly for diagnosis and staging around 1990, 30 years ago.

- Antibiotics versus No antibiotics or versus Alternative antibiotic regimen (for any patient)
    - Any class, route, treatment duration, or initiation time, and comparisons among these
    - Use of any antibiotics (e.g., at clinician's discretion) or specific antibiotics
- Interventional radiology procedure versus No procedure (conservative management; for patients with complicated diverticulitis for whom no procedure is an option)
    - Any interventional radiology procedure appropriate for the severity and type of complication
    - Exclude: Comparison of intervention radiology procedures or techniques

Outcomes:

- Short-term (≤30 days)
    - Resolution of diverticulitis
    - Return to normal bowel function
    - Length of hospital (or intensive care unit) stay
- Short- and medium-term (<1 year)
    - Interventional radiology procedure for diverticulitis (avoidance) (exclude for comparisons of interventional radiology procedure with conservative management)
- Any duration (short-, medium-, or long-term)
    - Conversion to complicated diverticulitis
    - Surgery for diverticulitis (avoidance)
        - Including colostomy (avoidance)
    - Rehospitalization for diverticulitis or complications
    - Quality of life/Functional outcomes
    - Resource use
    - Missed work, employment, school outcomes, etc.
    - Diverticulitis-related morbidities
    - Mortality, both diverticulitis-related and all-cause
- Medium- to long term (>1 month)
    - Recurrent diverticulitis
    - Opioid misuse
- All categorical "effectiveness" outcomes include time to outcome
- Harms, adverse events, side effects of interventions (any time frame)
    - Hospitalization comparison:
        - Hospital-based infections and other harms
    - Antibiotics comparisons:
        - Side effects/adverse events attributable to antibiotics
        - Clostridioides difficile (C diff) infection
        - Antibiotic resistance
    - Interventional radiology comparisons:
        - Adverse events related to procedures, including bleeding and catheter infections
        - Need for second procedures or revisions

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., prior history of diverticulitis, age)
- Presentation or course of illness (e.g., specific symptoms)
- Other factors (e.g., complicated or uncomplicated diverticulitis, hospital setting)

Timing:

- Minimum duration of follow-up = treatment duration (hospitalization, antibiotic use)

Setting:

- Inpatient, emergency department (or equivalent), outpatient

Design:

- Randomized controlled trials (all subquestions)
  - N≥10/arm
- Nonrandomized comparative studies
  - Restrict to studies that use modeling or other analytic methods to minimize selection bias (due to inherent differences between people who receive one or the other intervention), or that restrict study eligibility criteria such that comparisons being made are between patients with similar presentations.
  - N≥30/arm*
- Single group studies
  - Only for adverse events
  - N>100†
- Longitudinal (Exclude: cross-sectional)
- Prospective or retrospective
- Publication since 1990‡
- Exclude: Case reports (and series of case reports)

Study Eligibility Criteria for KQ 3 (Colonoscopy)

Population(s)

- Adults with history of (resolved) acute diverticulitis
- Exclude: Active diverticulitis
- Exclude: History of related condition (only), e.g., complicated diverticulosis, SUDD
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions:

- Elective colonoscopy (full colon)
- Elective CT colonography

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* The minimum sample size may be adjusted upward depending on the number of available studies.

† Restricting to studies with at least 100 participants (who all receive the same intervention) will allow estimates of adverse event rates to be precise to the nearest 1 percent.

‡ Older studies are of little relevance to contemporary practice given changes in diagnosis and management of acute diverticulitis (e.g., availability of co-interventions; changes in management of chronic diverticular disease; temporal changes in diet, antibiotic use, lifestyle factors, etc.).

Comparators:

- No colon cancer screening
- Flexible sigmoidoscopy and barium enema
- Limited colonoscopy (e.g., left-sided)
- Virtual colonoscopy
- Stool guaiac testing (etc.)
- Other colon cancer screens (e.g., DNA tests)
- Different intervals, Different initial colonoscopy timing after acute episode
- No comparator

Outcomes:

- Colorectal cancer
- Colonic premalignant lesions (e.g., hyperplastic polyps and adenomas)
- Colorectal cancer mortality
- Tolerance, feasibility, and completion of procedure; technical adequacy
- Harms, adverse events, and side effects of colonoscopy (e.g. perforation, bleeding)

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., age, family history)
- Course of illness (e.g., prior complicated vs. uncomplicated diverticulitis)
- Other factors (e.g., timing since last episode of acute diverticulitis)

Timing:

- Start of colorectal cancer screening after resolution of acute disease

Setting:

- Outpatient

Design:

- Randomized controlled trials
  - N≥10/arm
- Nonrandomized comparative studies
  - No restriction based on analytic methods
  - N≥10/arm*
- Single group studies
  - N≥20 (receiving colonoscopy or CT colonography)*
- Case-control studies
- Longitudinal (Exclude: cross-sectional)
- Prospective or retrospective
- Publication since 1990†
- Exclude: Case reports (and series of case reports)

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* The minimum sample size may be adjusted upward depending on the number of available studies.

† Older studies are of little relevance to contemporary practice given changes in diagnosis and management of acute diverticulitis (e.g., availability of co-interventions; changes in management of chronic diverticular disease; temporal changes in diet, antibiotic use, lifestyle factors, etc.).

Study Eligibility Criteria for KQ 4 (Prevention of recurrence)

Population(s):

- Adults with history of (resolved) acute diverticulitis
- Exclude: Ongoing acute diverticulitis
- Exclude: History of related condition (only), e.g., complicated diverticulosis, SUDD
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions:

- Pharmacological treatments
  - Any class, route, regimen, treatment duration, or initiation time
- Non-pharmacological interventions
  - Any class/type, route/method, regimen, treatment duration, or initiation time
- Elective surgery
  - Laparoscopic, open, robot-assisted, or any other type of colon surgery conducted as an elective (non-emergent) procedure
- Exclude: Natural history or undefined/unspecified intervention or undefined/unspecified comparator

Comparators:

- Pharmacological and non-pharmacological intervention comparisons:
  - Alternative pharmacologic or non-pharmacologic intervention (or regimen)
    - Pharmacologic vs. non-pharmacologic intervention
    - Other class/type
    - Other intervention within class/type
    - Same intervention different treatment duration
    - Same intervention, different initiation time
  - No intervention
    - Placebo
    - "Usual care" (needs to be defined)
- Elective surgery comparisons:
  - No or deferred elective surgery
  - Exclude: Comparisons with other surgical approaches or techniques
- All:
  - Exclude: Natural history or undefined/unspecified intervention or comparator

Outcomes:

- Recurrent diverticulitis
- Acute complicated diverticulitis
- Surgery for diverticulitis (avoidance; except for elective surgery comparisons)
  - Including colostomy (avoidance)
- Hospitalization for diverticulitis or diverticulitis-related complications (e.g., fistula, stricture)
- Quality of life/Functional outcomes
- All categorical "effectiveness" outcomes include time to outcome
- Harms, adverse events, or side effects of interventions (e.g., surgical complications)

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., age)

- Course of illness (e.g., prior complicated vs. uncomplicated diverticulitis)
- Other factors (e.g., time since last episode of diverticulitis)

Timing:

- No minimum duration of follow-up
- Hospitalization, unit stay, post-hospitalization

Setting:

- Inpatient, emergency department (or equivalent), outpatient

Design:

- Randomized controlled trials
  - N≥10/arm
- Nonrandomized comparative studies
  - Restrict to studies that use modeling or other analytic methods to minimize selection bias (due to inherent differences between people who receive one or the other intervention)
  - N≥30/arm*
- Single group studies
  - Only for adverse events
  - N>250†
- Longitudinal (Exclude: cross-sectional)
- Prospective or retrospective
- Publication since 1990‡
- Exclude: Case reports (and series of case reports)

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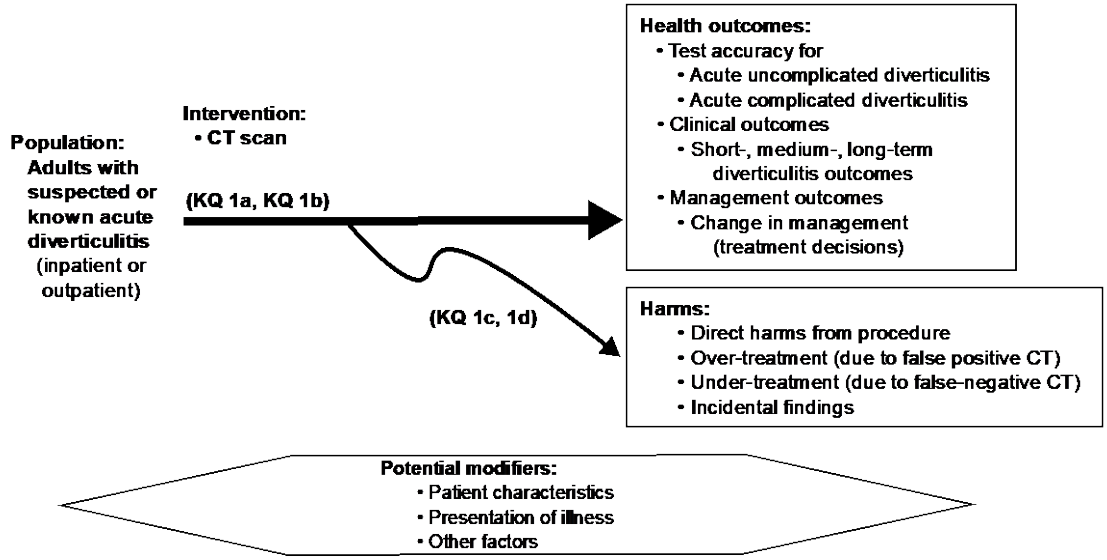
* The minimum sample size may be adjusted upward depending on the number of available studies.

† Restricting to larger studies will allow estimates of adverse event rates to be increasingly precise. Numerous single group studies of surgical harms exist, so we are restricting to the larger such studies.

‡ Older studies are of little relevance to contemporary practice given changes in diagnosis and management of acute diverticulitis (e.g., availability of co-interventions; changes in management of chronic diverticular disease; temporal changes in diet, antibiotic use, lifestyle factors, etc.).

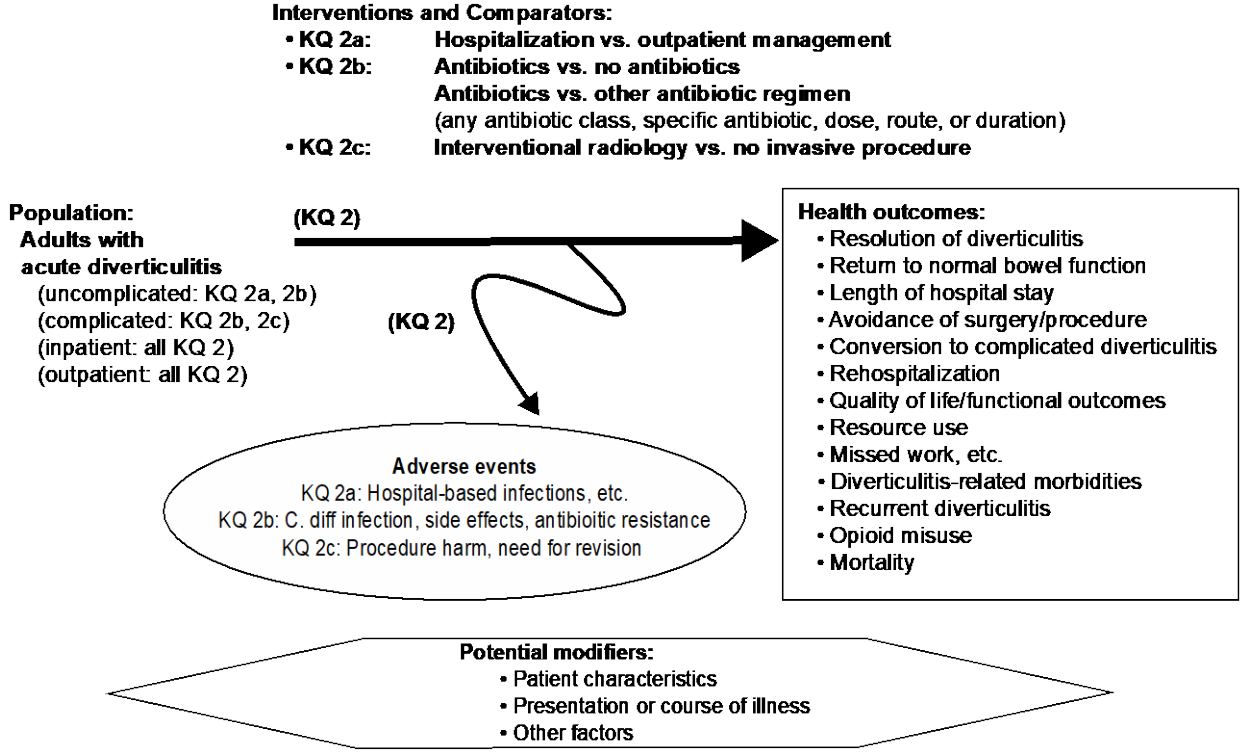
III. Analytic Frameworks

Figure 1. Analytic Framework for *Key Question 1*: CT for acute diverticulitis.



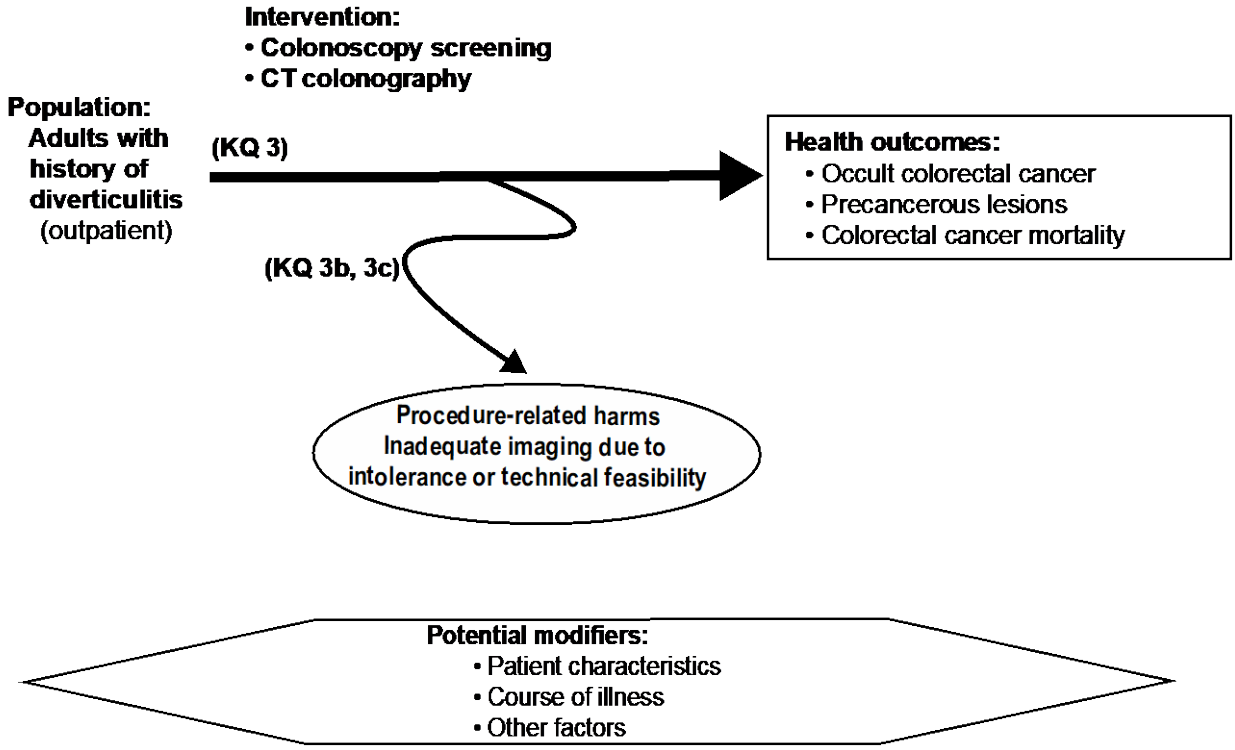
CT = computed tomography, KQ = Key Question, MRI = magnetic resonance imaging.

Figure 2. Analytic Framework for *Key Question 2*: Treatment options for acute diverticulitis.



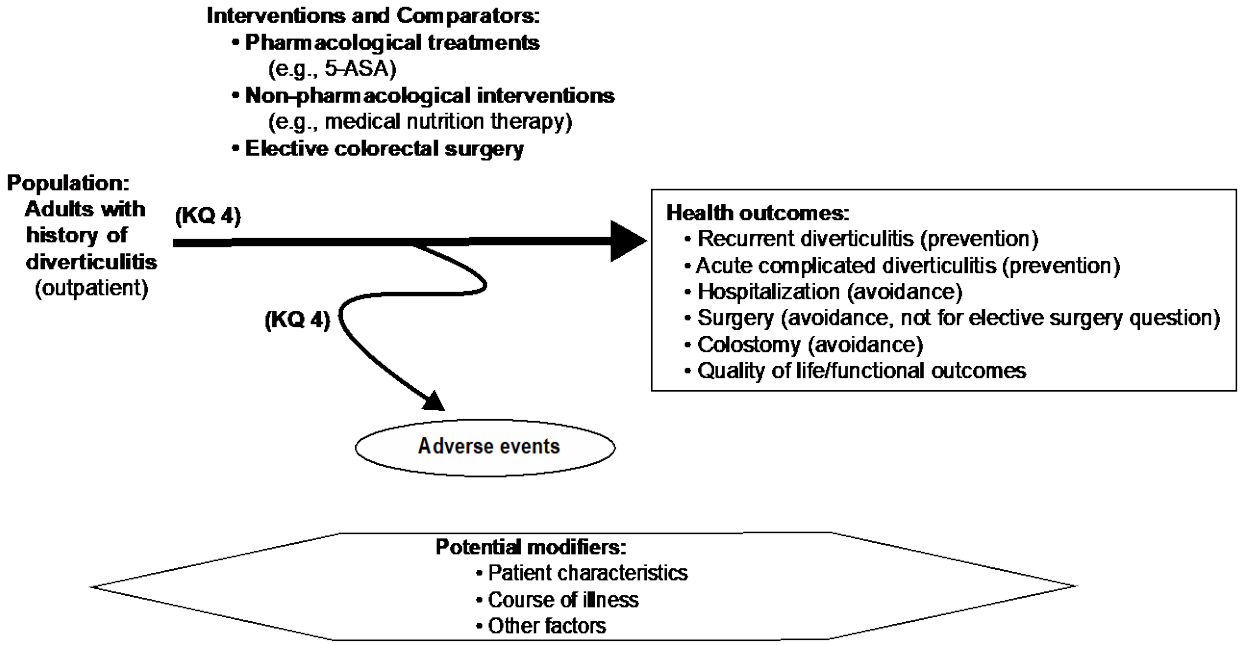
KQ = Key Question.

Figure 3. Analytic Framework for *Key Question 3*: Screening for colorectal cancer.



CT = computed tomography, KQ = Key Question.

Figure 4. Analytic Framework for *Key Question 4*: Treatments to prevent recurrent diverticulitis.



5-ASA = 5-aminosalicylic acid (also known as mesalamine or mesalazine), KQ = Key Question.

IV. Methods

The systematic review will Evidence-based Practice Center Program methodology, as laid out in its Methods Guide, particularly as pertain to reviews of comparative effectiveness, diagnostic tests, and complex meta-analyses.[48]

Criteria for Inclusion/Exclusion of Studies in the Review: See detailed PICOTS in section II.

Literature Search Strategies To Identify Relevant Studies to Answer the Key Questions: We will search for studies and existing systematic reviews in MEDLINE (via PubMed), The Cochrane Register of Clinical Trials, The Cochrane Database of Systematic Reviews, Embase, and CINAHL. Separate, overlapping searches will be conducted for each Key Question, then combined. Duplicate citations will be removed prior to screening. Searches will be restricted to 1990 or later, with no language restriction. (The date restriction is included after discussion with the Key Informants based on important changes in diagnosis and clinical management of diverticulitis based on increased use of CT imaging.) Search strategies include filters to remove nonhuman studies and articles that are not primary studies, systematic reviews, or clinical practice guidelines.

The searches include MeSH or Emtree terms, along with free-text words, related to diverticulitis, diverticulosis, and diverticular disease (since we have found that numerous articles misname or misclassify diverticulitis as diverticulosis); CT imaging; hospitalization, antibiotics, and interventional radiology for acute diverticulitis; colonoscopy and colonography; treatments to prevent recurrence and elective surgery. We will also search for CT imaging and acute abdomen (regardless of diverticular disease). The search strategy has been compared with the yield from the Topic Refinement phase of this review, which had included a broader search. As a part of an independent methods project, an interim search of MEDLINE will be undertaken by an independent librarian using text mining tools. Both searches will be independently peer reviewed. The planned MEDLINE search strategy is included in Appendix A; the strategies for other databases will be adapted from this strategy.

Searches will be conducted in the ClinicalTrials.gov registry for unpublished study protocols, unpublished study results, and ongoing studies. The reference lists of relevant existing systematic reviews will be screened for additional eligible studies. A Supplemental Evidence And Data for Systematic review (SEADS) portal will be available for this review. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria. Non-English language articles will be screened and data extracted either by readers of the relevant languages or after translation via Google Translate (https://translate.google.com/), if possible.

Searches will be updated during the public posting period.

Citations from all electronic databases will be entered into Abstrackr software (http://abstrackr.cebm.brown.edu/) to enable abstract screening. The team will conduct one or more rounds of pilot screening, during which each member of the team will screen the same 100 abstracts and discuss conflicts, with the goals of training the team in the nuances of the eligibility

criteria and refining them as needed. Thereafter, we will screen all remaining abstracts in duplicate. The Abstrackr software has machine learning capabilities that predict the likelihood of relevance of each citation. Daily, the list of unscreened abstracts will be sorted so that most potentially-relevant articles are presented first. This process will make screening more efficient and will enable us to capture the large majority of relevant articles relatively early in the abstract screening process.

Potentially relevant citations will be retrieved in full text. These articles will be rescreened in duplicate.

Data Extraction and Data Management: Eligible studies will be data extracted into the Systematic Review Data Repository-Plus (SRDR+) software. Each article will be extracted by one researcher and entered data will be confirmed by a second, independent researcher. Individual studies with multiple publications will be extracted as a single study (with a single entry in SRDR+). Each study will be entered into SRDR+ separately, even if two or more studies are reported within a single publication.

For each study, we will extract publication identifying data, study design features, population characteristics, intervention and comparator names and descriptions, relevant outcomes and their definitions, and funding source. In particular, we will extract, as available, data on stage and severity of acute diverticulitis (including specific diverticulitis complications), history of diverticulitis and prior treatments, and patient age and demographic features.

Assessment of Methodological Risk of Bias of Individual Studies: We will evaluate each study for risk of bias and methodological quality.

For randomized controlled trials, we will adapt the Cochrane Risk of Bias tool,[49] focusing on issues related to randomization and allocation concealment methodology; patient, caregiver, and outcome assessor blinding; loss to followup (omissions from analyses); adequacy of descriptions of study participants, interventions, and outcomes; and other issues. Questions related to outcome assessor blinding, loss to followup, and reporting adequacy will be assessed for each outcome.

For nonrandomized comparative studies, we will add assessments of specific elements from ROBINS-I,[50] in particular related to selection bias (comparability of groups). The questions will be assessed for each outcome (e.g., whether each outcome was adjusted for potential confounders).

For single group studies, we will primarily assess specific elements from ROBINS-I,[50] in particular related to selection bias (appropriateness of included participants) and completeness of outcome (primarily harms) reporting (for each outcome separately).

We will assess the adequacy of the existing systematic reviews based on the completeness (sensitivity) of their literature search methods, the appropriateness of their eligibility criteria, the statistical appropriateness of their meta-analyses and other analyses, and their evaluation of the study-level risk of bias.

Data Synthesis: We will summarize the evidence both qualitatively and, when feasible, quantitatively. Each study included in the *de novo* systematic review will be described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality. The existing systematic reviews (for CT test accuracy) will be summarized narratively regarding their

eligibility criteria, the included studies, and their conclusions. We will critique these reviews within the narrative. Summary tables will briefly describe the systematic reviews and their findings, as needed.

For Key Question 1a (test accuracy), we will focus on test sensitivity and specificity for diagnosis of acute diverticulitis, diagnosis of acute complicated (vs. uncomplicated) diverticulitis, and staging of the severity of acute diverticulitis. We will report results as per the existing systematic review

For Key Questions 1b and 1c, we will focus on event rates for clinical outcomes and of clinical management changes related to CT imaging. We expect to describe these results semiquantitatively (i.e., without meta-analysis), although if sufficient studies report sufficiently similar results, we will consider meta-analysis.

For Key Question 2, we will compare interventions (hospitalization, antibiotics, interventional radiology) to their comparators, for their effects, primarily with odds ratios (ORs) of event rates, "net differences" (between-intervention comparison of within-intervention changes) of continuous outcomes with both pre- and post-intervention data (e.g., pain or quality of life scales), and differences (between interventions) in continuous outcome data post-intervention (e.g., length of stay or days of missed work). Where there are sufficient studies reporting sufficiently similar results, we plan to meta-analyze these comparisons. If data allow, we also plan to conduct a Bayesian network meta-analysis comparing the different antibiotics to each other and to placebo (or no antibiotics). Depending on the evidence base, we may conduct separate analyses for acute uncomplicated and acute complicated diverticulitis. We expect to summarize harms data semiquantitatively (i.e., without meta-analysis).

For Key Question 3, we will focus on event rates of the clinical outcomes and harms. We expect to describe these results semiquantitatively (i.e., without meta-analysis), although if sufficient studies report sufficiently similar results, we will consider meta-analysis.

For Key Question 4, we will compare interventions (pharmacologic, nonpharmacologic, elective surgical) to their comparators, for their effects, primarily with ORs of event rates, "net differences" of continuous outcomes with both pre- and post-intervention data, and differences (between interventions) in continuous outcome data post-intervention. We plan to conduct a Bayesian network meta-analysis comparing the (nonsurgical) pharmacologic and nonpharmacologic interventions to each other and to placebo (or no intervention). We do not expect to include surgical interventions in this network meta-analysis since we expect the study designs, eligibility criteria, and outcomes to be too dissimilar to allow indirect statistical comparison. We expect to summarize elective surgical results and harms data semiquantitatively (i.e., without meta-analysis).

Across Key Questions, we expect to qualitatively describe reporting of differences in effects and harms by different factors, subgroups, or predictors. We do not expect to be able to conduct statistical analyses on these evaluations. We expect to primarily rely on reported within-study differences in effects (or harms). However, we will look for opportunities to qualitatively or quantitatively compare results across studies.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: Following AHRQ Methods guidance,[48] we will evaluate the strength of evidence (SoE) addressing each major comparison or evaluation for each Key Question. We expect that these will include:

- Test accuracy for
    - Diagnosing acute diverticulitis
    - Differentiating acute complicated from uncomplicated diverticulitis
    - Staging acute diverticulitis
- Effects of CT imaging on clinical outcomes and changes in clinical management
- Effects of false positive CT imaging on clinical outcomes
- Effects of false negative CT imaging on clinical outcomes
- Clinical effects of hospitalization versus outpatient care for acute uncomplicated diverticulitis
- Harms related to hospitalization versus outpatient care for acute uncomplicated diverticulitis
- Relative clinical effects of antibiotics for acute uncomplicated diverticulitis
- Relative clinical effects of antibiotics for acute complicated diverticulitis
- Harms related to antibiotics for acute diverticulitis
- Clinical effects of interventional radiology for acute complicated diverticulitis
- Harms related to interventional radiology for acute complicated diverticulitis
- Incidence of malignant and premalignant colon tumors found by colonoscopy
- Relative clinical effects of pharmacologic and nonpharmacologic interventions to prevent recurrent diverticulitis
- Harms of pharmacologic and nonpharmacologic interventions to prevent recurrent diverticulitis
- Clinical effects of elective surgery to prevent recurrent diverticulitis
- Harms related to elective surgery to prevent recurrent diverticulitis

We will discuss with the Technical Expert Panel (TEP) whether there are established minimal clinical important differences we can apply to our assessments of the SoE and related conclusions.

Assessing Applicability: For each Key Question (or specific subquestion), we will assess the applicability of the included studies primarily based on the studies' eligibility criteria and their included participants, specifically related to such factors as severity of disease, prior history, age, sex, and race/ethnicity. These will be qualitatively compared with typical distributions of these factors among people with diverticulitis in the U.S. We will also assess whether the interventions are available and currently used in the U.S. for treatment of diverticulitis. Other factors may include the age and geographic location of the study.

V. References

1. Shahedi K, Fuller G, Bolus R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clin Gastroenterol Hepatol. 2013 Dec;11(12):1609-13. doi: 10.1016/j.cgh.2013.06.020. PMID: 23856358.
2. Greenwood-Ericksen MB, Havens JM, Ma J, et al. Trends in Hospital Admission and Surgical Procedures Following ED visits for Diverticulitis. West J Emerg Med. 2016 Jul;17(4):409-17. doi: 10.5811/westjem.2016.4.29757. PMID: 27429691.
3. Bollom A, Austrie J, Hirsch W, et al. Emergency Department Burden of Diverticulitis in the USA, 2006-2013. Dig Dis Sci. 2017 Oct;62(10):2694-703. doi: 10.1007/s10620-017-4525-y. PMID: 28332105.
4. Shah SD, Cifu AS. Management of Acute Diverticulitis. Jama. 2017 Jul 18;318(3):291-2. doi: 10.1001/jama.2017.6373. PMID: 28719679.
5. Strate LL, Modi R, Cohen E, et al. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012 Oct;107(10):1486-93. doi: 10.1038/ajg.2012.194. PMID: 22777341.
6. Lin MP, Weissman J, Sinnette C, et al. 87 Prioritizing Conditions for Which to Compare Emergency Department Admission Rates. Annals of Emergency Medicine. 2014 2014/10/01/;64(4, Supplement):S31-S2. doi: 10.1016/j.annemergmed.2014.07.112.
7. Buchs NC, Konrad-Mugnier B, Jannot AS, et al. Assessment of recurrence and complications following uncomplicated diverticulitis. Br J Surg. 2013 Jun;100(7):976-9; discussion 9. doi: 10.1002/bjs.9119. PMID: 23592303.
8. Lahat A, Avidan B, Sakhnini E, et al. Acute diverticulitis: a decade of prospective follow-up. J Clin Gastroenterol. 2013 May-Jun;47(5):415-9. doi: 10.1097/MCG.0b013e3182694dbb. PMID: 23328302.
9. Lameris W, van Randen A, Bipat S, et al. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. Eur Radiol. 2008 Nov;18(11):2498-511. doi: 10.1007/s00330-008-1018-6. PMID: 18523784.
10. Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management -- a prospective study of 542 patients. Eur Radiol. 2002 May;12(5):1145-9. doi: 10.1007/s00330-001-1143-y. PMID: 11976860.
11. Kaiser AM, Jiang JK, Lake JP, et al. The management of complicated diverticulitis and the role of computed tomography. Am J Gastroenterol. 2005 Apr;100(4):910-7. doi: 10.1111/j.1572-0241.2005.41154.x. PMID: 15784040.
12. Klarenbeek BR, de Korte N, van der Peet DL, et al. Review of current classifications for diverticular disease and a translation into clinical practice. Int J Colorectal Dis. 2012 Feb;27(2):207-14. doi: 10.1007/s00384-011-1314-5. PMID: 21928041.
13. Hughes ES, Cuthbertson AM, Carden AB. The surgical management of acute diverticulitis. Med J Aust. 1963 May 25;50(1):780-2. PMID: 13955553.
14. Kohler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. Surg Endosc. 1999 Apr;13(4):430-6. PMID: 10094765.
15. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85-109. PMID: 735943.
16. Wasvary H, Turfah F, Kadro O, et al. Same hospitalization resection for acute diverticulitis. Am Surg. 1999 Jul;65(7):632-5; discussion 6. PMID: 10399971.

17. Hansen O, Graupe F, Stock W. [Prognostic factors in perforating diverticulitis of the large intestine]. Chirurg. 1998 Apr;69(4):443-9. PMID: 9612631.
18. Kruse E, Leifeld L. Prevention and Conservative Therapy of Diverticular Disease. Viszeralmedizin. 2015 Apr;31(2):103-6. doi: 10.1159/000377651. PMID: 26989379.
19. Sartelli M, Moore FA, Ansaloni L, et al. A proposal for a CT driven classification of left colon acute diverticulitis. World J Emerg Surg. 2015;10:3. doi: 10.1186/1749-7922-10-3. PMID: 25972914.
20. Nally DM, Kavanagh DO. Current Controversies in the Management of Diverticulitis: A Review. Dig Surg. 2018 Apr 19. doi: 10.1159/000488216. PMID: 29672283.
21. Isacson D, Andreasson K, Nikberg M, et al. No antibiotics in acute uncomplicated diverticulitis: does it work? Scand J Gastroenterol. 2014 Dec;49(12):1441-6. doi: 10.3109/00365521.2014.968861. PMID: 25369865.
22. Biondo S, Golda T, Kreisler E, et al. Outpatient versus hospitalization management for uncomplicated diverticulitis: a prospective, multicenter randomized clinical trial (DIVER Trial). Ann Surg. 2014 Jan;259(1):38-44. doi: 10.1097/SLA.0b013e3182965a11. PMID: 23732265.
23. Schug-Pass C, Geers P, Hugel O, et al. Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis. Int J Colorectal Dis. 2010 Jun;25(6):751-9. doi: 10.1007/s00384-010-0899-4. PMID: 20140619.
24. Chabok A, Pahlman L, Hjern F, et al. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012 Apr;99(4):532-9. doi: 10.1002/bjs.8688. PMID: 22290281.
25. Daniels L, Unlu C, de Korte N, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017 Jan;104(1):52-61. doi: 10.1002/bjs.10309. PMID: 27686365.
26. Mege D, Yeo H. Meta-analyses of Current Strategies to Treat Uncomplicated Diverticulitis. Dis Colon Rectum. 2019 Mar;62(3):371-8. doi: 10.1097/dcr.0000000000001295. PMID: 30570549.
27. Garfinkle R, Kugler A, Pelsser V, et al. Diverticular Abscess Managed With Long-term Definitive Nonoperative Intent Is Safe. Dis Colon Rectum. 2016 Jul;59(7):648-55. doi: 10.1097/dcr.0000000000000624. PMID: 27270517.
28. Ritz JP, Lehmann KS, Frericks B, et al. Outcome of patients with acute sigmoid diverticulitis: multivariate analysis of risk factors for free perforation. Surgery. 2011 May;149(5):606-13. doi: 10.1016/j.surg.2010.10.005. PMID: 21145569.
29. Hall JF, Roberts PL, Ricciardi R, et al. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? Dis Colon Rectum. 2011 Mar;54(3):283-8. doi: 10.1007/DCR.0b013e3182028576. PMID: 21304297.
30. Li D, Baxter NN, McLeod RS, et al. The Decline of Elective Colectomy Following Diverticulitis: A Population-Based Analysis. Dis Colon Rectum. 2016 Apr;59(4):332-9. doi: 10.1097/dcr.0000000000000561. PMID: 26953992.
31. Elagili F, Stocchi L, Ozuner G, et al. Outcomes of percutaneous drainage without surgery for patients with diverticular abscess. Dis Colon Rectum. 2014 Mar;57(3):331-6. doi: 10.1097/DCR.0b013e3182a84dd2. PMID: 24509455.
32. Harisinghani MG, Gervais DA, Hahn PF, et al. CT-guided transgluteal drainage of deep pelvic abscesses: indications, technique, procedure-related complications, and clinical outcome. Radiographics. 2002 Nov-Dec;22(6):1353-67. doi: 10.1148/rg.226025039. PMID: 12432107.

33. Lopez-Borao J, Kreisler E, Millan M, et al. Impact of age on recurrence and severity of left colonic diverticulitis. Colorectal Dis. 2012 Jul;14(7):e407-12. doi: 10.1111/j.1463-1318.2012.02976.x. PMID: 22321968.
34. Ritz JP, Lehmann KS, Stroux A, et al. Sigmoid diverticulitis in young patients--a more aggressive disease than in older patients? J Gastrointest Surg. 2011 Apr;15(4):667-74. doi: 10.1007/s11605-011-1457-2. PMID: 21318443.
35. Brandl A, Kratzer T, Kafka-Ritsch R, et al. Diverticulitis in immunosuppressed patients: A fatal outcome requiring a new approach? Can J Surg. 2016 Aug;59(4):254-61. doi: 10.1503/cjs.012915. PMID: 27240131.
36. Yoo PS, Garg R, Salamone LF, et al. Medical comorbidities predict the need for colectomy for complicated and recurrent diverticulitis. Am J Surg. 2008 Nov;196(5):710-4. doi: 10.1016/j.amjsurg.2008.07.017. PMID: 18954602.
37. Carabotti M, Annibale B, Severi C, et al. Role of Fiber in Symptomatic Uncomplicated Diverticular Disease: A Systematic Review. Nutrients. 2017 Feb 20;9(2). doi: 10.3390/nu9020161. PMID: 28230737.
38. Stollman N, Smalley W, Hirano I. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015 Dec;149(7):1944-9. doi: 10.1053/j.gastro.2015.10.003. PMID: 26453777.
39. Iannone A, Ruospo M, Wong G, et al. Mesalazine for People with Diverticular Disease: A Systematic Review of Randomized Controlled Trials. Can J Gastroenterol Hepatol. 2018;2018:5437135. doi: 10.1155/2018/5437135. PMID: 30320044.
40. Agarwal AK, Karanjawala BE, Maykel JA, et al. Routine colonic endoscopic evaluation following resolution of acute diverticulitis: is it necessary? World J Gastroenterol. 2014 Sep 21;20(35):12509-16. doi: 10.3748/wjg.v20.i35.12509. PMID: 25253951.
41. Balthazar EJ, Megibow A, Schinella RA, et al. Limitations in the CT diagnosis of acute diverticulitis: comparison of CT, contrast enema, and pathologic findings in 16 patients. AJR Am J Roentgenol. 1990 Feb;154(2):281-5. doi: 10.2214/ajr.154.2.2105015. PMID: 2105015.
42. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 1999 Nov;94(11):3110-21. doi: 10.1111/j.1572-0241.1999.01501.x. PMID: 10566700.
43. Sharma PV, Eglinton T, Hider P, et al. Systematic review and meta-analysis of the role of routine colonic evaluation after radiologically confirmed acute diverticulitis. Ann Surg. 2014 Feb;259(2):263-72. doi: 10.1097/sla.0000000000000294. PMID: 24169174.
44. Chabok A, Smedh K, Nilsson S, et al. CT-colonography in the follow-up of acute diverticulitis: patient acceptance and diagnostic accuracy. Scand J Gastroenterol. 2013 Aug;48(8):979-86. doi: 10.3109/00365521.2013.809597. PMID: 23834748.
45. Effective Health Care Program. Management of Acute Diverticulitis. https://effectivehealthcare.ahrq.gov/get-involved/nominated-topics/management-acute-diverticulitis. 2018.
46. Effective Health Care Program. Management of Acute Diverticulitis Topic Nomination. https://effectivehealthcare.ahrq.gov/system/files/docs/acute-diverticulitis-topic-nomination.pdf. 2018.
47. American College of Physicians. Guideline Process: How Does ACP Develop Clinical Recommendations? https://www.acponline.org/clinical-information/guidelines/guideline-process. 2019.

48. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. . Rockville, MD: Agency for Healthcare Research and Quality; 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
49. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
50. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. bmj. 2016;355:i4919.

VI. Definition of Terms and Abbreviations

C. diff	Clostridioides difficile infection, a difficult-to-treat bacterial infection that occurs in people on long-term (or repeated courses) of antibiotics.
Colonoscopy	endoscopy procedure to visualize the colon, used to screen for colorectal cancer and precancerous lesions
Complicated diverticulitis	a bout of diverticulitis with evidence of an abscess, other pericolonic infection, perforation, or fistula; usually associated with fever and/or blood in the stool.
CT	computed tomography
CT colonography	a CT procedure to visualize the interior wall of the colon, used when colonoscopy not feasible
Diverticular disease	the constellation of symptomatic and asymptomatic diverticulosis and diverticulitis; in research studies, the term is most commonly used to mean non-diverticulitis, such as in "symptomatic uncomplicated diverticular disease"
Diverticulitis	herein referring to colonic diverticulitis; inflammation of outpouchings (diverticula) of the wall of the large intestine
Diverticulosis	presence of diverticula (outpouchings) of the wall of the large intestine; may be symptomatic but without evidence of inflammation.
Incidental finding (on CT)	CT finding of a potential lesion or abnormality unrelated to the reason for conducting the test. For example, a kidney mass found on a CT done to confirm diverticulitis.
KQ	Key Question
NRCS	nonrandomized comparative study
RCT	randomized controlled trial
SoE	strength of evidence
SR	systematic review (a protocolized review of the evidence base)

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants (KIs)

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

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

X. Technical Expert Panel (TEP)

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft

report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

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

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290201500002I (Task Order #13) from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).