National Institute for Health and Care Excellence

Consultation

Diverticular disease

B. Evidence review: Symptoms and signs of diverticular disease

NICE guideline

Prognostic evidence review

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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1. Diverticular Disease

1.1 Review question: What symptoms and signs indicate diverticular disease as a possible diagnosis?

1.2 Introduction

Symptoms and signs of diverticular disease such as change in bowel habit, abdominal pain and rectal bleeding can be very similar to those of other bowel pathologies such as cancer and inflammatory bowel disease. It is therefore important that the clinician has a good understanding of the disease and its differential diagnosis so as to ensure a correct diagnosis is made. Usually the diagnosis of diverticular disease is not made purely on symptoms alone, further assessment and investigations will need to be undertaken to confirm this. This question aimed to review the evidence of which symptoms indicate a possible diagnosis of diverticular disease.

1.3 PICO table

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over with suspected diverticular disease.
Prognostic variable(s) under consideration	• Abdominal pain • Change in bowel habit • Bloating • Rectal bleeding • Any combinations of the above
Confounding factors	• Age • Gender
Outcome	• Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve • Relative risk (RR) • Diagnosis of Diverticular disease
Study design	• Cohort studies • Cross-sectional studies

1.4 Clinical evidence

1.4.1 Included studies

One study was included in the review;[41] this is summarised in the clinical evidence summary (Table 2) below.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

A search was conducted for RCTs and observational studies investigating the association of the following factors: abdominal pain, change in bowel habit, bloating, rectal bleeding and any combination of these factors in adults people suspected with diverticular disease.

No relevant studies were identified for diverticular disease, however one study has been included for people with suspected diverticulosis. This study has been downgraded accordingly for indirectness.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations/notes
Nagata 2015[41]	People with diverticulosis compared to people without diverticulosis	Multivariate analysis- logistic regression	Abdominal pain (discomfort) Change in bowel habit (constipation, diarrhoea, loose stools, hard stools)	Age, sex, BMI, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidaemia	Bowel symptoms for diverticulosis	Case-control study Japanese population

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Diverticulosis

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Abdominal discomfort in people with diverticulosis compared to a control population without diverticulosis	1	Adjusted OR: 1.03 (0.93-1.14) [a]	Serious[b]	VERY LOW[c]
Constipation in people with diverticulosis compared to a control population without diverticulosis	1	Adjusted OR: 0.85 (0.78 to 0.93) [a]	None	VERY LOW[c]
Diarrhoea in people with diverticulosis compared to a control population without diverticulosis	1	Adjusted OR: 1.02 (0.93 to 1.12) [a]	Serious[b]	VERY LOW[c]
Loose stool in people with diverticulosis compared to a control population without diverticulosis	1	Adjusted OR: 1.03 (0.93 to 1.14) [a]	Serious[b]	VERY LOW[c]
Hard stool in people with diverticulosis compared to a control population without diverticulosis	1	Adjusted OR: 0.89 (0.78 to 1.02) [a]	Serious[b]	VERY LOW[c]

(a) Methods: multivariable analysis, adjusted for age, sex, BMI, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidaemia.
(b) Imprecision was considered serious if the confidence intervals crossed the line of null effect.
(c) Downgraded by 1 increment as study outcome was Diverticulosis

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6 Evidence statements

1.6.1 Clinical evidence statements

One case-control study of 1629 people with or without diverticulosis showed, in multivariate analysis, that abdominal discomfort, constipation, diarrhoea, loose stool and hard stool were not clinically important predictors of diverticulosis (very low quality).

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 Review question: In which people with suspected diverticular disease should investigations be performed?

1.8 Introduction

Most patients with diverticulosis remain asymptomatic, and in these the diagnosis of uncomplicated colonic diverticula is made only when the patient has incidental investigations for unrelated symptoms, e.g. computed tomography of the abdomen or colonoscopy for unrelated symptoms, or for bowel cancer screening. Typical symptoms of diverticular disease include abdominal pain, usually in the left iliac fossa, and a change in bowel habit predominantly to constipation or to looser bowel motions. Rectal bleeding may also occur if a colonic vessel is eroded in a diverticulum. At first presentation, the differential diagnosis for these symptoms includes a wide range of other conditions, including irritable bowel syndrome, inflammatory bowel disease, colorectal cancer, and, in females, ovarian or other gynaecological pathologies. In addition, the average age of presentation of diverticular disease is in the early sixties[44], many such patients will fulfil referral criteria referral for suspected colorectal cancer. In younger patients, diagnosis of diverticular disease may be delayed unless symptoms are investigated, which would not usually be indicated for patients presenting with abdominal pain alone. This chapter seeks to establish the optimal approach to investigation of patients presenting with typical symptoms of diverticular disease.

1.9 PICO table

For full details see the review protocol in Appendix I.

Table 4: PICO characteristics of review question

Population	Adults aged 18 years and over with suspected diverticular disease

Prognostic variables under consideration	• Stricture
	• Fistula
	• Perforation
	• Abscess
	• Other conditions:
	  ○ Cancer
	  ○ Inflammatory bowel disease
	  ○ IBS
	  ○ UTI
	  ○ Endometriosis
	  ○ Ovarian cyst

Confounding factors	• Age • Gender
Outcomes	• Diagnosis of Diverticular disease • Diagnosis of Diverticulitis • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve • Relative risk (RR)
Study design	• Cohort studies • Cross-sectional studies

1.10 Clinical evidence

1.10.1 Included studies

Three studies were included in the review;[29, 34, 51] these are summarised in Table 5 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 6 and Table 7).

See also the study selection flow chart in appendix J, study evidence tables in appendix K, forest plots in appendix L and GRADE tables in appendix M.

1.10.2 Excluded studies

See the excluded studies list in appendix N.

Summary of clinical studies included in the evidence review

Table 5: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variable	Confounders	Outcomes	Limitations
Jung 2010[29]	Random samples, stratified by age and gender, of the residents of Olmsted County between 1988 and 1993. Subjects were classified as having IBS based on the symptoms recorded in a self-reported questionnaire. Diagnosis of diverticular disease established by any positive colon test (colonoscopy, flexible sigmoidoscopy, abdomen CT and/or CT colonography, or barium enema). Total cohort = 1712 People with IBS n = 223	Logistic regression analyses, adjusting for age and gender.	IBS	Age Gender	Diverticular disease	Risk of bias: very high Demographics/ event rate for control (non-IBS) group not reported
Lee 2012[34]	Subjects undergoing CT colonography, divided into two groups: those with proven colorectal cancer (case group) and those with no colorectal cancer (control group) matched for age and gender. Case group n= 302 Control group n=302	Univariate analysis; Chi-square test.* *groups were matched for age and gender.	Colorectal cancer	Age Gender	Diverticulosis	Risk of bias: high Control group: asymptomatic control, undergoing CT for screening examination.
Sirinthornpunya	Patients aged 18 and over with	Univariate	IBS	Age	Diverticular	Risk of bias: very

Study	Population	Analysis	Prognostic variable	Confounders	Outcomes	Limitations
2014[51]	clinical physical examination compatible with IBS. Control group were patients aged 18 and over who received colonoscopy for various indications. Case group n=75 Control group n=75	analysis; student t-test.* *no difference in age, sex and BMI between the IBS and the control groups (p>0.05)		Gender	disease	high Control group: received colonoscopy for various indications.

See appendix K for full evidence tables.

Quality assessment of clinical studies included in the evidence review

Table 6: Clinical evidence summary: Colorectal cancer

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Risk of diverticulosis in people with colorectal cancer compared to a control population with no cancer.	1	OR: 0.78 (0.54 to 1.11) [a]	Serious[b]	VERY LOW[c]

(a) Methods: multivariable analysis, adjusted for age & sex.
(b) Imprecision was considered serious if the confidence intervals crossed the line of null effect.
(c) Downgraded by 1 increment as study outcome was Diverticulosis. Downgraded by 1 increment as study was at high risk of bias.

Table 7: Clinical evidence summary: IBS

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Risk of diverticular disease in people with IBS compared to a control population with no IBS.	2	OR: 1.8 (1.3 to 2.54) [a]	None[b]	LOW[c]

(a) Methods: univariate analysis, matched for age & sex.
(b) Imprecision was considered serious if the confidence intervals crossed the line of null effect.
(c) Downgraded by 1 increment as study was at high risk of bias.

See appendix M for full GRADE tables.

1.11 Economic evidence

1.11.1 Included studies

No relevant health economic studies were identified.

1.11.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.12 Evidence statements

1.12.1 Clinical evidence statements

One case-control study of 604 people, matched for age and gender, showed that there was no clinically significant risk of diverticulosis in people with colorectal cancer (very low quality).

Two studies in people with or without IBS showed that IBS was not a clinically important risk factor for diverticular disease (n=1862, very low quality).

1.12.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.13 Recommendations

Diverticular disease

B1. Suspect diverticular disease if a person presents with one or both of the following:

- intermittent abdominal pain in the left lower quadrant with constipation, diarrhoea or occasional large rectal bleeds (the pain may be triggered by eating and relieved by the passage of stool or flatus)
- tenderness in the left lower quadrant on abdominal examination.

Be aware that in a minority of people and in people of Asian origin, pain and tenderness may be localised in the right lower quadrant.

1.13.1 Research recommendations

No recommendations were made.

1.14 Rationale and impact

1.14.1 Why the committee made the recommendations

Diverticular disease

The evidence on signs and symptoms comprised a single study with no clinically important outcomes and was based on a population with diverticulitis rather than diverticular disease. Because of a lack of evidence, recommendations were made using formal consensus methods and the knowledge and expertise of the committee on the most common presentation of diverticular disease (see Chapter R for more details). The majority of people experience pain on the left side of the abdomen where the diverticula most often occur in the sigmoid colon. For this reason people are often tender on the left lower quadrant. However, it was important to highlight that people of Asian origin may experience right-sided symptoms. Other symptoms are variable but people experience constipation, diarrhoea or both with occasional rectal bleeds. The symptoms alone are not specific enough to indicate diverticular disease but should be considered in conjunction with intermittent abdominal pain.

1.14.2 Impact of the recommendations on practice

The recommendation reflects current practice.

1.15 The committee's discussion of the evidence

1.15.1 Interpreting the evidence

1.15.2 The outcomes that matter most

The committee highlighted the importance of reporting both the prognostic outcomes of diagnosis of diverticular disease, as well as the diagnostic accuracy outcomes such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), receiver operating characteristic (ROC) curve or area under curve, and relative risk (RR) where studies reported these.

1.15.3 The quality of the evidence

The quality of evidence ranged from very low to low. This was mostly due to selection and performance bias, resulting in a high risk of bias rating, and imprecision. Outcomes were downgraded where they included an indirect population or reported an indirect outcome, including where diagnosis of diverticulosis was reported as opposed to the desired diagnosis of diverticular disease.

1.15.4 Benefits and harms

The committee discussed the evidence on the signs and symptoms for diagnosing diverticular disease (2.1) and the indications for investigation for suspected diverticular disease (2.2).

There was only one study included in review 2.1, however this was on an indirect population looking at the diagnosis of diverticulosis. The risk factors assessed did not show any positive association to diverticulosis, however there were negative associations of diverticulosis to the prognostic factors constipation and hard stool. The committee felt that given the lack of direct evidence for this review, it would not be possible to make any recommendations.

For review 2.2, the evidence presented demonstrated a negative prognostic association between a diagnosis of colorectal cancer and diagnosis of diverticular disease, although the committee noted the serious imprecision associated with the outcome. The committee also discussed the apparent predictive value of a diagnosis of IBS for a further diagnosis of diverticular disease. The committee highlighted that the focus of this area lies on the prognostic value of a suspicion of the noted predictive factors and subsequent investigation i.e. cancer or IBS, rather than a diagnosis of them. Given this, the committee agreed that the findings may not provide sufficient guidance on the review question and subsequently are insufficient to form a recommendation.

It is expected that the overlap of symptoms between the suggested prognostic factors and diverticular disease should lead to investigation.

1.15.5 Cost effectiveness and resource use

No relevant economic evaluations were identified which address which signs and symptoms indicate diverticular disease as a possible diagnosis (2.1) or which people with suspected diverticular disease should be investigated further (2.2). There were no relevant unit costs to consider for either review question.

The committee noted that the signs and symptoms of diverticular disease are not specific to the disease, but are common to many bowel conditions. As a result, the diagnosis of diverticular disease is usually acquired incidentally through investigation for several bowel conditions with overlapping symptom profiles, for example colorectal cancer. The costs of the investigations are not attributable to the diverticular disease population alone.

No evidence of clinical or cost effectiveness was found, so recommendations were made by a Delphi panel and minor edits made by the Committee. The cost-effectiveness of investigating symptoms is not known. However, the recommendation does not represent a move away from current practice.

1.15.6 Other factors the committee took into account

The study providing evidence for review question 2.1 was based on a Japanese population which the committee felt may not be comparable to the UK population given differences in lifestyle, particularly with differences between western and Asian diets.

From the Delphi survey, consensus was reached on the main symptoms of diverticular disease. The majority of people experience pain on the left side of the abdomen where the diverticula most often occur. For this reasons people are often tender on the left lower quadrant. However, it was important to highlight that people of Asian origin may experience right sided symptoms. Other symptoms are variable but people experience constipation, diarrhoea or both with occasional rectal bleeds. Alone the symptoms are not specific enough to indicate diverticular disease but should be considered in conjunction with intermittent abdominal pain.

The statements on bloating and the passage of mucus rectally were removed from the survey. Respondents either indicated that this was a non-specific symptom or was more likely to indicate irritable bowel disorder or inflammatory disease. The committee considered that these symptoms were not specific enough to indicate diverticular disease and the corresponding statements were removed from the guideline.

References

1. Abi-Hanna P, Gleckman R. Acute abdominal pain: A medical emergency in older patients. Geriatrics. 1997; 52(7):72-4

2. Alexandersson BT, Hreinsson JP, Stefansson T, Jonasson JG, Bjornsson ES. The risk of colorectal cancer after an attack of uncomplicated diverticulitis. Scandinavian Journal of Gastroenterology. 2014; 49(5):576-80

3. Alli O, Smith C, Hoffman M, Amanullah S, Katz P, Amanullah AM. Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel. Journal of Clinical Gastroenterology. 2011; 45(5):410-414

4. Ambrosetti P, Robert J, Witzig JA, Mirescu D, de Gautard R, Borst F et al. Prognostic factors from computed tomography in acute left colonic diverticulitis. British Journal of Surgery. 1992; 79(2):117-9

5. Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H et al. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Digestive Surgery. 2013; 30(4-6):278-92

6. Arora G, Mannalithara A, Mithal A, Triadafilopoulos G, Singh G. Concurrent conditions in patients with chronic constipation: A population-based study. PloS One. 2012; 7(10):e42910

7. Bielecki K, Kaminski P, Klukowski M. Large bowel perforation: morbidity and mortality. Techniques in Coloproctology. 2002; 6(3):177-82

8. Binda GA, Amato A, Serventi A, Arezzo A. Clinical presentation and risks. Digestive Diseases. 2012; 30(1):100-107

9. Birris T. An uncommon cause of abdominal pain: Mucinous adenocarcinoma with signet ring cell features arising from a Meckel's diverticulum. American Journal of Gastroenterology. 2010; 105:S242

10. Braunschmid T, Stift A, Mittlbock M, Lord A, Weiser FA, Riss S. Constipation is not associated with diverticular disease - Analysis of 976 patients. International Journal of Surgery. 2015; 19:42-5

11. Carpenter WS, Allaben RD, Kambouris AA. Fistulas complicating diverticulitis of the colon. Surgery, Gynecology and Obstetrics. 1972; 134(4):625-8

12. Cazacu M, Dejica D, Badea R, Secas N, Tudose M, Ban A. Colorectal cancer and pre-existing pathological conditions: Ulcerative colitis, Crohn's disease, colonic diverticulosis and polyposis. A retrospective analysis of 286 surgical patients. Romanian Journal of Gastroenterology. 1997; 6(4):239-241

13. Cervellin G, Mora R, Ticinesi A, Meschi T, Comelli I, Catena F et al. Epidemiology and outcomes of acute abdominal pain in a large urban emergency department: retrospective analysis of 5,340 cases. Annals of Translational Medicine. 2016; 4(19):362

14. Chang SS, Huang N, Hu HY. Patients with end-stage renal disease were at an increased risk of hospitalization for acute diverticulitis. Medicine. 2016; 95(39):e4881

15. Choung RS, Rey E, Locke GR, Schleck CD, Baum C, Zinsmeister AR et al. Chronic constipation and co-morbidities: A prospective population-based nested case-control study. United European Gastroenterology Journal. 2016; 4(1):142-151

16. Del Rio P, Rossini M, Papadia C, Lorenzo V, Labonia D, Sianesi M. Diverticular disease and colon cancer: a real association between the two diseases? Annali Italiani di Chirurgia. 2014; 85(4):389-96

17. Foster KJ, Holdstock G, Whorwell PJ, Guyer P, Wright R. Prevalence of diverticular disease of the colon in patients with ischaemic heart disease. Gut. 1978; 19(11):1054-6

18. Granlund J, Svensson T, Granath F, Hjern F, Ekbom A, Blomqvist P et al. Diverticular disease and the risk of colon cancer - a population-based case-control study. Alimentary Pharmacology and Therapeutics. 2011; 34(6):675-81

19. Gryspeerdt S, Lefere P. Chronic diverticulitis vs. colorectal cancer: Findings on CT colonography. Abdominal Imaging. 2012; 37(6):1101-1109

20. Havia T, Manner R. The irritable colon syndrome. A follow-up study with special reference to the development of diverticula. Acta Chirurgica Scandinavica. 1971; 137(6):569-72

21. Huang V, Habal F. Diverticular disease-associated segmental colitis: A 14 year follow up. Gastroenterology. 2012; 142(1):S450

22. Huang W, Jen Y, Chang Y, Hsiao C, Yang M, Lin C et al. Association between colonic diverticular disease and colorectal cancer: A nationwide population-based study. Clinical Gastroenterology and Hepatology. 2014; 12(8):1288-1294

23. Hwang JA, Kim SM, Song HJ, Lee YM, Moon KM, Moon CG et al. Differential diagnosis of left-sided abdominal pain: primary epiploic appendagitis vs colonic diverticulitis. World Journal of Gastroenterology. 2013; 19(40):6842-8

24. Inoue M, Kubo A, Munakata A. Epidemiological studies on diverticular disease of the colon in Japan. Journal of the Japan Society of Colo-Proctology. 1980; 33(5):521

25. Iyer R, Longstreth GF, Chu LH, Chen W, Yen L, Hodgkins P et al. Acute colonic diverticulitis: diagnostic evidence, demographic and clinical features in three practice settings. Journal of Gastrointestinal and Liver Diseases. 2014; 23(4):379-86

26. Jamal Talabani A, Endreseth BH, Lydersen S, Edna TH. Clinical diagnostic accuracy of acute colonic diverticulitis in patients admitted with acute abdominal pain, a receiver operating characteristic curve analysis. International Journal of Colorectal Disease. 2017; 32(1):41-7

27. Jaung R, Kularatna M, Robertson JP, Vather R, Rowbotham D, MacCormick AD et al. Uncomplicated acute diverticulitis: Identifying risk factors for severe outcomes. World Journal of Surgery. 2017; 41(9):2258-65

28. Jearwattanakanok K, Yamada S, Suntornlimsiri W, Smuthtai W, Patumanond J. Clinical scoring for diagnosis of acute lower abdominal pain in female of reproductive age. Emergency Medicine International. 2013; 2013:730167

29. Jung HK, Choung RS, Locke GR, 3rd, Schleck CD, Zinsmeister AR, Talley NJ. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: a population-based study. American Journal of Gastroenterology. 2010; 105(3):652-61

30. Jung S, Lee H, Chung H, Park JC, Shin SK, Lee SK et al. Incidence and predictive factors of irritable bowel syndrome after acute diverticulitis in Korea. International Journal of Colorectal Disease. 2014; 29(11):1369-76

31. Kawatkar A, Chu LH, Iyer R, Yen L, Chen W, Erder MH et al. Development and validation of algorithms to identify acute diverticulitis. Pharmacoepidemiology and Drug Safety. 2015; 24(1):27-37

32. Kim SY, Oh TH, Seo JY, Jeon TJ, Seo DD, Shin WC et al. The clinical factors for predicting severe diverticulitis in Korea: a comparison with Western countries. Gut & Liver. 2012; 6(1):78-85

33. Lee KM, Paik CN, Chung WC, Jung SH, Chang UI, Yang JM. Clinical significance of colonic diverticulosis associated with bowel symptoms and colon polyp. Journal of Korean Medical Science. 2010; 25(9):1323-9

34. Lee SJ, Kim SA, Ku BH, Kim HY, Kim JY, Chang DK et al. Association between colorectal cancer and colonic diverticulosis: case-control study based on computed tomographic colonography. Abdominal Imaging. 2012; 37(1):70-3

35. Lewis LM, Banet GA, Blanda M, Hustey FM, Meldon SW, Gerson LW. Etiology and clinical course of abdominal pain in senior patients: a prospective, multicenter study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2005; 60(8):1071-6

36. Maconi G. Diagnosis of symptomatic uncomplicated diverticular disease and the role of Rifaximin in management. Acta Bio-Medica de l Ateneo Parmense. 2017; 88(1):25-32

37. Meeson S, Alvey CM, Golding SJ. Justifying multidetector CT in abdominal sepsis: time for review? British Journal of Radiology. 2009; 82(975):190-197

38. Meyer J, Thomopoulos T, Usel M, Gjika E, Bouchardy C, Morel P et al. The incidence of colon cancer among patients diagnosed with left colonic or sigmoid acute diverticulitis is higher than in the general population. Surgical Endoscopy. 2015; 29(11):3331-7

39. Morini S, de Angelis P, Manurita L, Colavolpe V. Association of colonic diverticula with adenomas and carcinomas. A colonoscopic experience. Diseases of the Colon and Rectum. 1988; 31(10):793-6

40. Mounce LTA, Price S, Valderas JM, Hamilton W. Comorbid conditions delay diagnosis of colorectal cancer: a cohort study using electronic primary care records. British Journal of Cancer. 2017; 116(12):1536-1543

41. Nagata N, Niikura R, Aoki T, Shimbo T, Sekine K, Okubo H et al. Association between colonic diverticulosis and bowel symptoms: A case-control study of 1629 Asian patients. Journal of Gastroenterology and Hepatology. 2015; 30(8):1252-9

42. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

43. Newhall SC, Lucas CE, Ledgerwood AM. Diagnostic and therapeutic approach to colonic bleeding. American Surgeon. 1981; 47(3):136-42

44. Nguyen GC, Sam J, Anand N. Epidemiological trends and geographic variation in hospital admissions for diverticulitis in the United States. World Journal of Gastroenterology. 2011; 17(12):1600-5

45. Niikura R, Nagata N, Akiyama J, Shimbo T, Uemura N. Hypertension and concomitant arteriosclerotic diseases are risk factors for colonic diverticular bleeding:

a case-control study. International Journal of Colorectal Disease. 2012; 27(9):1137-43

46. Oistamo E, Hjern F, Blomqvist L, Von Heijne A, Abraham-Nordling M. Cancer and diverticulitis of the sigmoid colon. Differentiation with computed tomography versus magnetic resonance imaging: preliminary experiences. Acta Radiologica. 2013; 54(3):237-41

47. Otte JJ, Larsen L, Andersen JR. Irritable bowel syndrome and symptomatic diverticular disease--different diseases? American Journal of Gastroenterology. 1986; 81(7):529-31

48. Peery AF, Sandler RS, Ahnen DJ, Galanko JA, Holm AN, Shaukat A et al. Constipation and a low-fiber diet are not associated with diverticulosis. Clinical Gastroenterology and Hepatology. 2013; 11(12):1622-7

49. Sallinen V, Mentula P, Leppaniemi A. Risk of colon cancer after computed tomography-diagnosed acute diverticulitis: is routine colonoscopy necessary? Surgical Endoscopy. 2014; 28(3):961-6

50. Singh A, Baptista V, Stoicov C, Cave DR. Evaluation of small bowel bleeding. Current Opinion in Gastroenterology. 2013; 29(2):119-124

51. Sirinthornpunya S, Rungjiratananon S. Association of colonic diverticular disease and irritable bowel syndrome in Thai patients. Journal of the Medical Association of Thailand. 2014; 97 (Suppl 11):S18-24

52. Spiller R, Humes D, Richards M, Hastings M, Neal K, Whorwell P. Somatisation predicts symptom severity and consulting behaviour in irritable bowel syndrome patients and those with symptomatic diverticular disease. Gut. 2009; 58(Suppl 1):A104

53. Staniland JR, Ditchburn J, De Dombal FT. Clinical presentation of acute abdomen: study of 600 patients. BMJ. 1972; 3(5823):393-8

54. Stefansson T, Ekbom A, Sparen P, Pahlman L. Cancers among patients diagnosed as having diverticular disease of the colon. European Journal of Surgery. 1995; 161(10):755-60

55. Stefansson T, Ekbom A, Sparen P, Pahlman L. Association between sigmoid diverticulitis and left-sided colon cancer: A nested, population-based, case control study. Scandinavian Journal of Gastroenterology. 2004; 39(8):743-747

56. Stromberg C, Johansson G, Adolfsson A. Acute abdominal pain: diagnostic impact of immediate CT scanning. World Journal of Surgery. 2007; 31(12):2347-54; discussion 2355-8

57. Sultan K, Fields S, Panagopoulos G, Korelitz BI. The nature of inflammatory bowel disease in patients with coexistent colonic diverticulosis. Journal of Clinical Gastroenterology. 2006; 40(4):317-21

58. Tan JP, Barazanchi AW, Singh PP, Hill AG, Maccormick AD. Predictors of acute diverticulitis severity: A systematic review. International Journal of Surgery. 2016; 26:43-52

59. Tursi A, Elisei W, Picchio M. Incidence and prevalence of inflammatory bowel diseases in gastroenterology primary care setting. European Journal of Internal Medicine. 2013; 24(8):852-6

60. Wilcox CM, Clark WS. Causes and outcome of upper and lower gastrointestinal bleeding: the Grady Hospital experience. Southern Medical Journal. 1999; 92(1):44-50

61. Wong ER, Idris F, Chong CF, Telisinghe PU, Tan J, Chong VH. Diverticular disease and colorectal neoplasms: Association between left sided diverticular disease with colorectal cancers and right sided with colonic polyps. Asian Pacific Journal of Cancer Prevention. 2016; 17(5):2401-5

62. Zuccaro G. Epidemiology of lower gastrointestinal bleeding. Best Practice & Research in Clinical Gastroenterology. 2008; 22(2):225-32

Appendices

Appendix A: Review protocols

Table 8: Review protocol: Symptoms and signs for diverticular disease

Field	Content
Review question	What symptoms and signs indicate diverticular disease as a possible diagnosis?
Type of review question	Diagnostic/Prognostic review : A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine which signs and symptoms indicate diverticular disease as a possible diagnosis
Eligibility criteria – population / disease / condition / issue / domain	Adults aged 18 years and over with suspected diverticular disease.
Eligibility criteria –/ intervention(s)/ exposures(s)/ prognostic factor(s)	• Abdominal pain • Change in bowel habit • Bloating • Rectal bleeding • Any combinations of the above
Eligibility criteria – confounders	• Age • Gender
Outcomes and prioritisation	• Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve • Relative risk (RR) • Diagnosis of Diverticular disease
Eligibility criteria – study design	Cohort studies Cross-sectional studies Studies will only be included if all the key confounders have been accounted for in a multivariate analysis.
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger • Prevention
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups: • People of Asian family origin as they are known to develop right-sided diverticula • Transplant patients/ immunocompromised
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.

Data management (software)	• The methodological quality of each study will be assessed using the adjusted QUIPS checklist. • Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.

Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 9: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[42] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with

	explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 11 of 12 CENTRAL to 2018 Issue 11 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Table 11: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/

15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	randomized controlled trial.pt.
23.	controlled clinical trial.pt.
24.	randomi#ed.ti,ab.
25.	placebo.ab.
26.	randomly.ti,ab.
27.	Clinical Trials as topic.sh.
28.	trial.ti.
29.	or/22-28
30.	Meta-Analysis/
31.	exp Meta-Analysis as Topic/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/50-59
41.	Epidemiologic studies/
42.	Observational study/
43.	exp Cohort studies/
44.	(cohort adj (study or studies or analys* or data)).ti,ab.
45.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
46.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
47.	Controlled Before-After Studies/
48.	Historically Controlled Study/
49.	Interrupted Time Series Analysis/
50.	(before adj2 after adj2 (study or studies or data)).ti,ab.
51.	or/30-39
52.	exp case control study/
53.	case control*.ti,ab.
54.	or/41-42
55.	40 or 43
56.	Cross-sectional studies/

57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/45-46
59.	40 or 47
60.	40 or 43 or 47
61.	21 and (29 or 40 or 60)

Table 12: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	random*.ti,ab.
21.	factorial*.ti,ab.
22.	(crossover* or cross over*).ti,ab.
23.	((doubl* or singl*) adj blind*).ti,ab.
24.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
25.	crossover procedure/
26.	single blind procedure/
27.	randomized controlled trial/
28.	double blind procedure/
29.	or/20-28
30.	systematic review/
31.	meta-analysis/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/30-39
41.	Clinical study/
42.	Observational study/
43.	family study/
44.	longitudinal study/
45.	retrospective study/
46.	prospective study/
47.	cohort analysis/
48.	follow-up/
49.	cohort*.ti,ab.
50.	48 and 49
51.	(cohort adj (study or studies or analys* or data)).ti,ab.
52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	(before adj2 after adj2 (study or studies or data)).ti,ab.
55.	or/41-47,50-54
56.	exp case control study/
57.	case control*.ti,ab.
58.	or/56-57
59.	55 or 58
60.	cross-sectional study/
61.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	or/60-61
63.	55 or 62
64.	55 or 58 or 62
65.	19 and (29 or 40 or 64)

Table 13: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Diverticular Disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions

Database	Dates searched	Search filter used
		Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 November 2018 NHSEED - Inception to March 2015	None

Table 15: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	Economics/
23.	Value of life/
24.	exp "Costs and Cost Analysis"/
25.	exp Economics, Hospital/
26.	exp Economics, Medical/
27.	Economics, Nursing/
28.	Economics, Pharmaceutical/
29.	exp "Fees and Charges"/
30.	exp Budgets/

31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/22-37
39.	exp models, economic/
40.	*Models, Theoretical/
41.	markov chains/
42.	monte carlo method/
43.	exp Decision Theory/
44.	(markov* or monte carlo).ti,ab.
45.	econom* model*.ti,ab.
46.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
47.	Models, Organizational/
48.	*models, statistical/
49.	*logistic models/
50.	models, nursing/
51.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
52.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
53.	(SSM or SODA).ti,ab.
54.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
55.	soft systems method*.ti,ab.
56.	(Meta-heuristic* or Metaheuristic*).ti,ab.
57.	(dynamic* adj2 (model* or system*)).ti,ab.
58.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
59.	(microsimulation* or "micro* simulation*").ti,ab.
60.	((flow or core) adj2 model*).ti,ab.
61.	(data adj2 envelopment*).ti,ab.
62.	system* model*.ti,ab.
63.	or/41-64
64.	quality-adjusted life years/
65.	sickness impact profile/
66.	(quality adj2 (wellbeing or well being)).ti,ab.
67.	sickness impact profile.ti,ab.
68.	disability adjusted life.ti,ab.
69.	(qal* or qtime* or qwb* or daly*).ti,ab.
70.	(euroqol* or eq5d* or eq 5*).ti,ab.
71.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
72.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
73.	(hui or hui1 or hui2 or hui3).ti,ab.
74.	(health* year* equivalent* or hye or hyes).ti,ab.

75.	discrete choice*.ti,ab.
76.	rosser.ti,ab.
77.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
78.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
79.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
80.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
81.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
82.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
83.	or/22-40
84.	21 and (38 or 63 or 83)

Table 16: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	Economics/
21.	Value of life/
22.	exp "Costs and Cost Analysis"/
23.	exp Economics, Hospital/
24.	exp Economics, Medical/
25.	Economics, Nursing/
26.	Economics, Pharmaceutical/
27.	exp "Fees and Charges"/
28.	exp Budgets/
29.	budget*.ti,ab.
30.	cost*.ti.

31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/20-35
37.	statistical model/
38.	*theoretical model/
39.	nonbiological model/
40.	stochastic model/
41.	decision theory/
42.	decision tree/
43.	exp nursing theory/
44.	monte carlo method/
45.	(markov* or monte carlo).ti,ab.
46.	econom* model*.ti,ab.
47.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
48.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
49.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
50.	(SSM or SODA).ti,ab.
51.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
52.	soft systems method*.ti,ab.
53.	(Meta-heuristic* or Metaheuristic*).ti,ab.
54.	(dynamic* adj2 (model* or system*)).ti,ab.
55.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
56.	(microsimulation* or "micro* simulation*").ti,ab.
57.	((flow or core) adj2 model*).ti,ab.
58.	(data adj2 envelopment*).ti,ab.
59.	system* model*.ti,ab.
60.	or/39-61
61.	quality adjusted life year/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

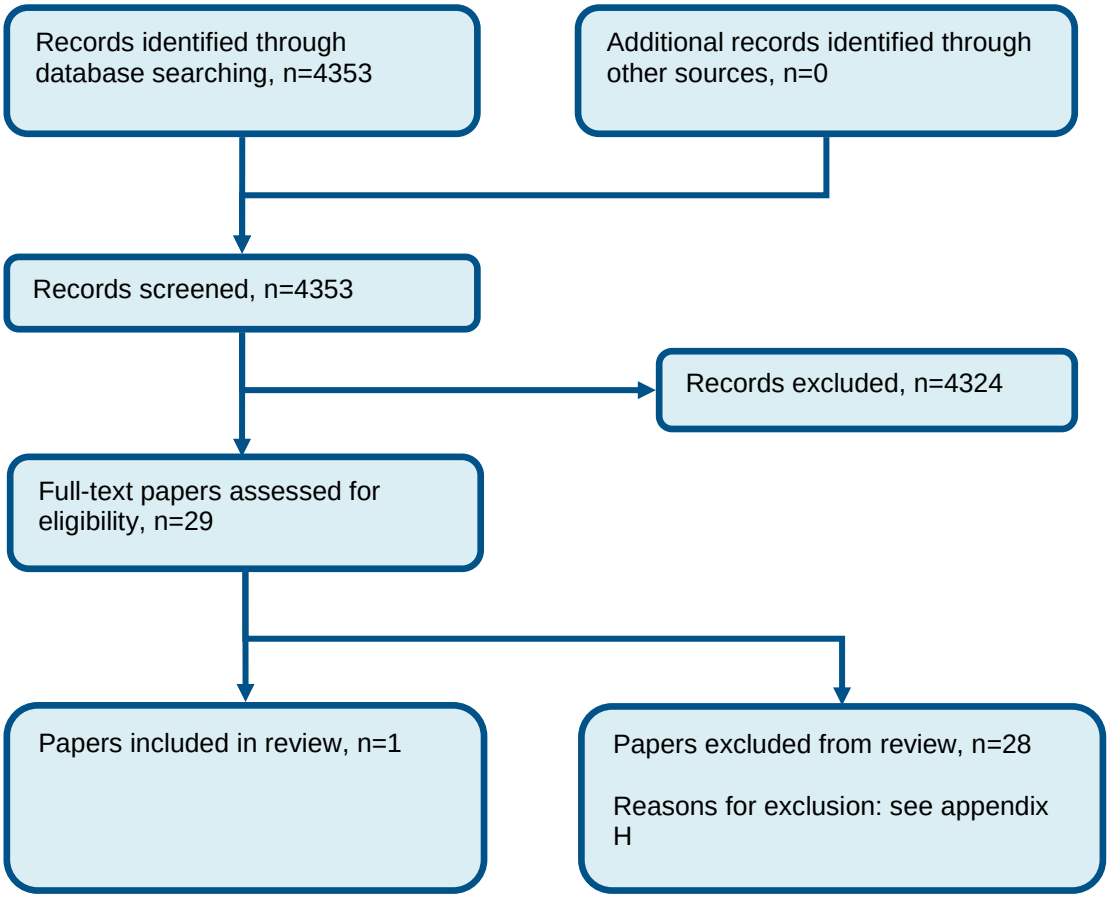
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/20-40
83.	19 and (36 or 60 or 82)

Table 17: NHS EED and HTA (CRD) search terms

#1.	diverticul*

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of symptoms and signs for diverticular disease



Appendix D: Clinical evidence tables

Table 18: Clinical evidence tables

Reference	Nagata 2015[41]
Study type and analysis	Case-control study with multivariable analysis
Number of participants and characteristics	Data source/ Recruitment: Patients scheduled to undergo elective colonoscopy between January 2012 and April 2014 n = 1629 (case n=543, control n=1086) Age (range): 40-79 years Gender (% men): case= 72.2%, control 70.9% Ethnicity: Japanese nationality Setting: Hospital Country: Japan Inclusion criteria: Adults ages between 40 and 79 years, Japanese nationality, undergoing endoscopy for colorectal adenoma/cancer screening or surveillance for polyps after resection of colorectal adenoma with or without gastrointestinal (GI) symptoms and patients with diverticulosis. Exclusion criteria: Unknown use of medications, previous urgent or early onset colonoscopy for acute onset of GI symptoms, previous history of GI resection, inability to undergo total colonoscopy, diverticula in the presence of macroscopically overt colitis or diverticulitis on colonoscopy, history of acute diverticulitis or presence of organic disease identified by colonoscopy with other imaging modalities.
Target condition(s)	Diverticular disease
Prognostic	Abdominal discomfort

Reference	Nagata 2015[41]
factors and confounders	Constipation Diarrhoea Loose stools Hard stools
Confounders OR Stratification strategy	Adjusted for age, sex, BMI, smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidaemia
Outcomes sizes and effects	Adjusted odds ratio (95% CIs): Abdominal discomfort: 1.03 (0.93-1.14) Constipation: 0.85 (0.78- 0.93) Diarrhoea: 1.02 (0.93- 1.11) Loose stool: 1.03 (0.93- 1.14) Hard stool: 0.89 (0.78- 0.94)
Comments	Risk of bias rating: Abdominal discomfort: High Constipation: High Diarrhoea: High Loose stool: High Hard stool: High

Appendix E: Forest plots

E.1 Symptoms and signs of diverticular disease

Diverticulosis

Figure 2: Abdominal pain

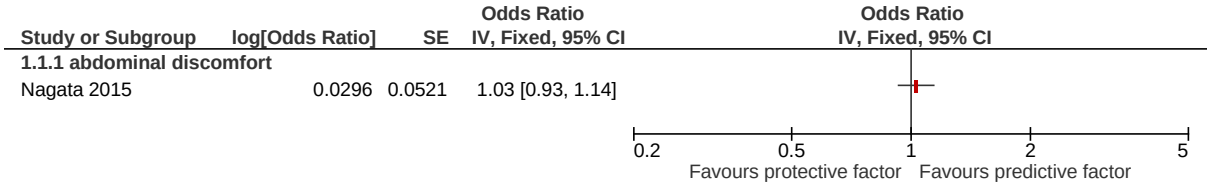
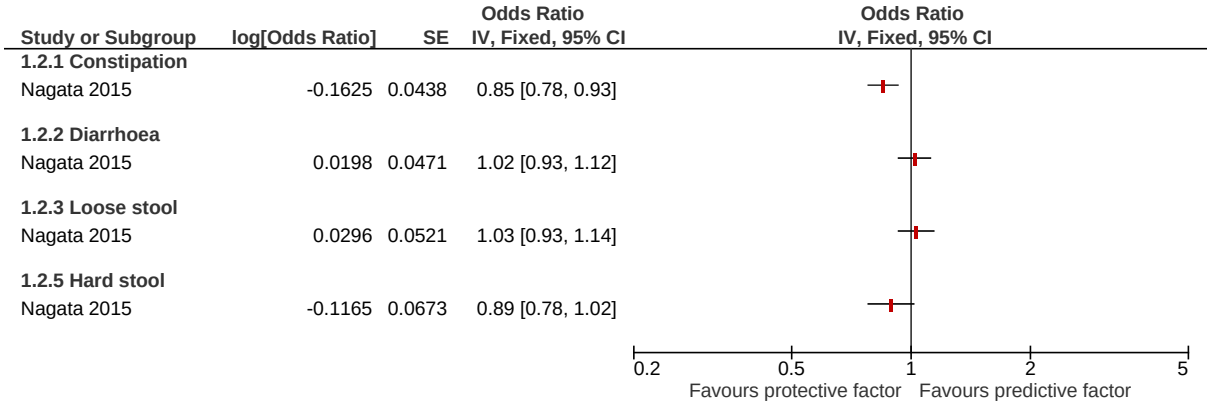


Figure 3: Change in bowel habit



Appendix F: GRADE tables

Table 19: Clinical evidence profile: Diverticulosis

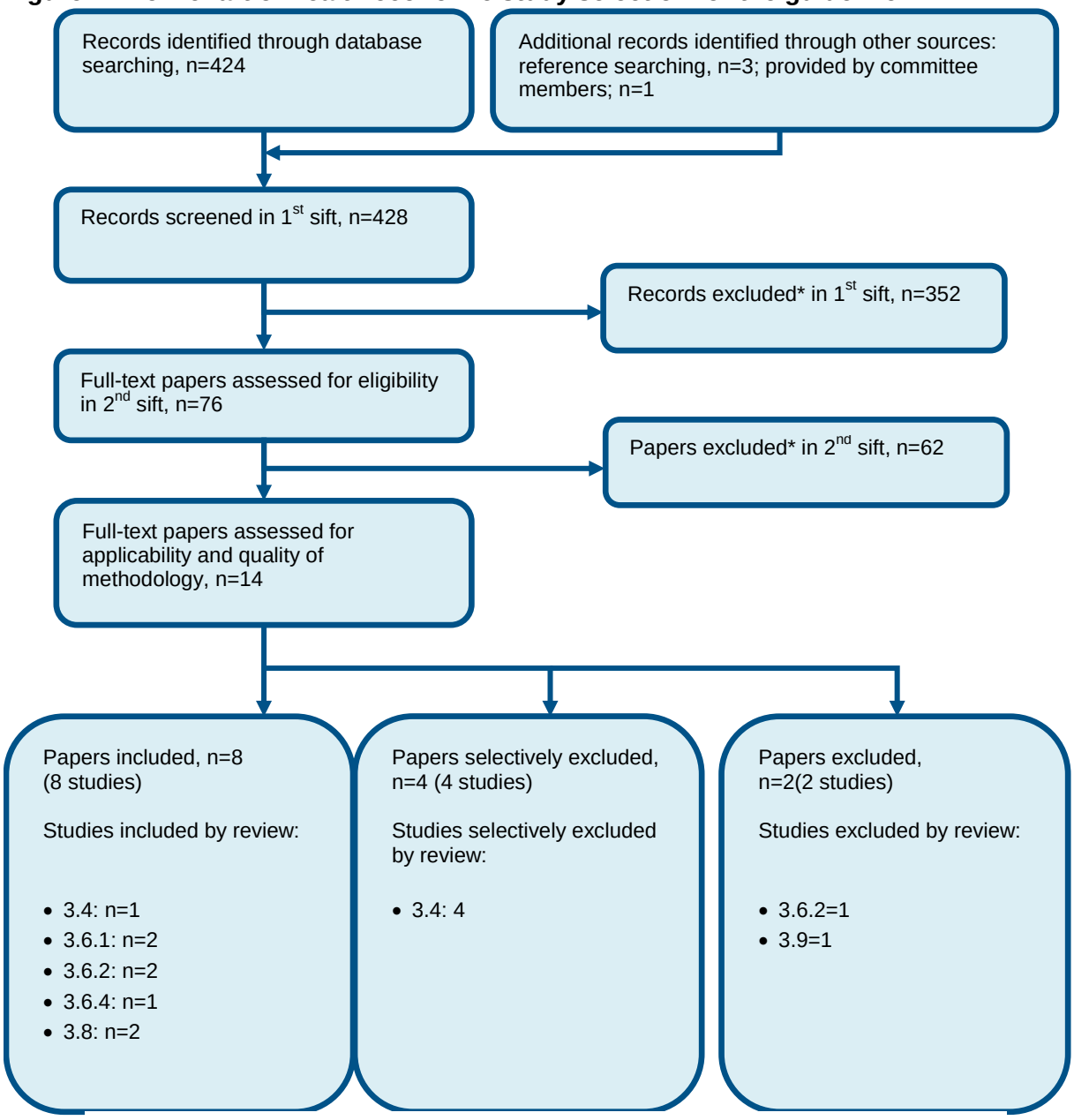
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Symptoms and signs for Diverticulosis	Control	Relative (95% CI)	Absolute		
Abdominal Pain - abdominal discomfort												
1	observational studies[2]	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	543 cases 1086 controls		OR 1.03 (0.93 to 1.14)	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Change in bowel habit - Constipation												
1	observational studies[2]	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	543 cases 1086 controls		OR 0.85 (0.78 to 0.93)	-	⊕OOO VERY LOW	CRITICAL
								-		-		
								0%		-		
Change in bowel habit - Diarrhoea												
1	observational studies[2]	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	543 cases 1086 controls		OR 1.02 (0.93 to 1.12)	-	⊕OOO VERY LOW	CRITICAL
								-		-		
								0%		-		
Change in bowel habit - Loose stool												

1	observational studies[2]	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	543 cases 1086 controls		OR 1.03 (0.93 to 1.14)	-	⊕OOO VERY LOW	CRITICAL
								-		-		
								0%		-		
Change in bowel habit - Hard stool												
1	observational studies[2]	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	543 cases 1086 controls		OR 0.89 (0.78 to 1.02)	-	⊕OOO VERY LOW	CRITICAL
								-		-		
								0%		-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] case-control study design
[3] Downgraded by 1 increment as the study outcome was Diverticulosis
[4] Imprecision was considered serious as the confidence interval crossed the line of null effect.

Appendix G: Health economic evidence selection

Figure 4: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3.4 Non-surgical treatment of acute diverticulitis (Evidence review H)

3.6.1 Timing of surgery (Evidence review J)

3.6.2 Laparoscopic versus open resection (Evidence review K)

3.6.4 Primary versus secondary anastomosis (Evidence review M)

3.8 Laparoscopic lavage versus resection for perforated diverticulitis (Evidence review O)

3.9 Management of recurrent diverticulitis (Evidence review P)

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 20: Studies excluded from the clinical review

Reference	Reason for exclusion
Abi-Hanna 1997[1]	Incorrect study design
Alli 2011[3]	Incorrect population and study design
Arora 2012[6]	Incorrect study design and population
Birris 2010[9]	Conference abstract
Braunschmid 2015[10]	No relevant outcomes
Cervellin 2016 [13]	Incorrect population
Choung 2016[15]	Incorrect study design and population
Huang 2012[21]	Conference abstract
Hwang 2013[23]	Incorrect population
Inoue 1980[24]	Conference abstract
Iyer 2014[25]	Incorrect population
Jamal Talabani 2017[26]	No relevant outcomes
Jaung 2017[27]	No relevant outcomes
Jearwattanakanok 2013[28]	Incorrect population
Kawatkar 2015[31]	No relevant results
Kim 2012[32]	Incorrect population
Lee 2010[33]	No relevant outcomes
Lewis 2005[35]	No relevant outcomes
Newhall 1981[43]	No relevant outcomes
Nguyen 2011[44]	No relevant outcomes
Peery 2013[48]	Incorrect population
Singh 2013[50]	Incorrect study design
Spiller 2009[52]	Conference abstract
Staniland 1972[53]	No relevant outcomes
Stromberg 2007[56]	No relevant outcomes
Tan 2016[58]	Incorrect population
Wilcox 1999[60]	Incorrect population
Zuccaro 2008[62]	Incorrect study design

Appendix I: Review protocols

Table 21: Review protocol: Indications for investigation for diverticular disease

Review question	In which people with suspected diverticular disease should investigations be performed?
Type of review question	Diagnostic/prognostic review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine which symptoms and signs indicate investigation for diverticular disease is appropriate.
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with suspected diverticular disease

Eligibility criteria – Intervention(s)/ exposure(s)/ prognostic factor(s)	• Stricture
	• Fistula
	• Perforation
	• Abscess
	• Other conditions:
	  ○ Cancer
	  ○ Inflammatory bowel disease
	  ○ IBS
	  ○ UTI
	  ○ Endometriosis
	  ○ Ovarian cyst

Eligibility criteria – Confounders	• Age • Gender
Outcomes and prioritisation	• Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve • Relative risk (RR) • Diagnosis of Diverticular disease • Diagnosis of Diverticulitis
Eligibility criteria – study design	Cohort studies Cross-sectional studies Note: Studies will only be included if all the key confounders have been accounted for in a multivariate analysis.
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger • Prevention
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups: • People of Asian family origin as they are known to develop right-sided diverticula

	• Transplant patients/ immunocompromised
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• The methodological quality of each study will be assessed using the adjusted QUIPS checklist. • Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where

	appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered
Review question	In which people with suspected diverticular disease should investigations be performed?

1 **Table 22: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[42] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and

	methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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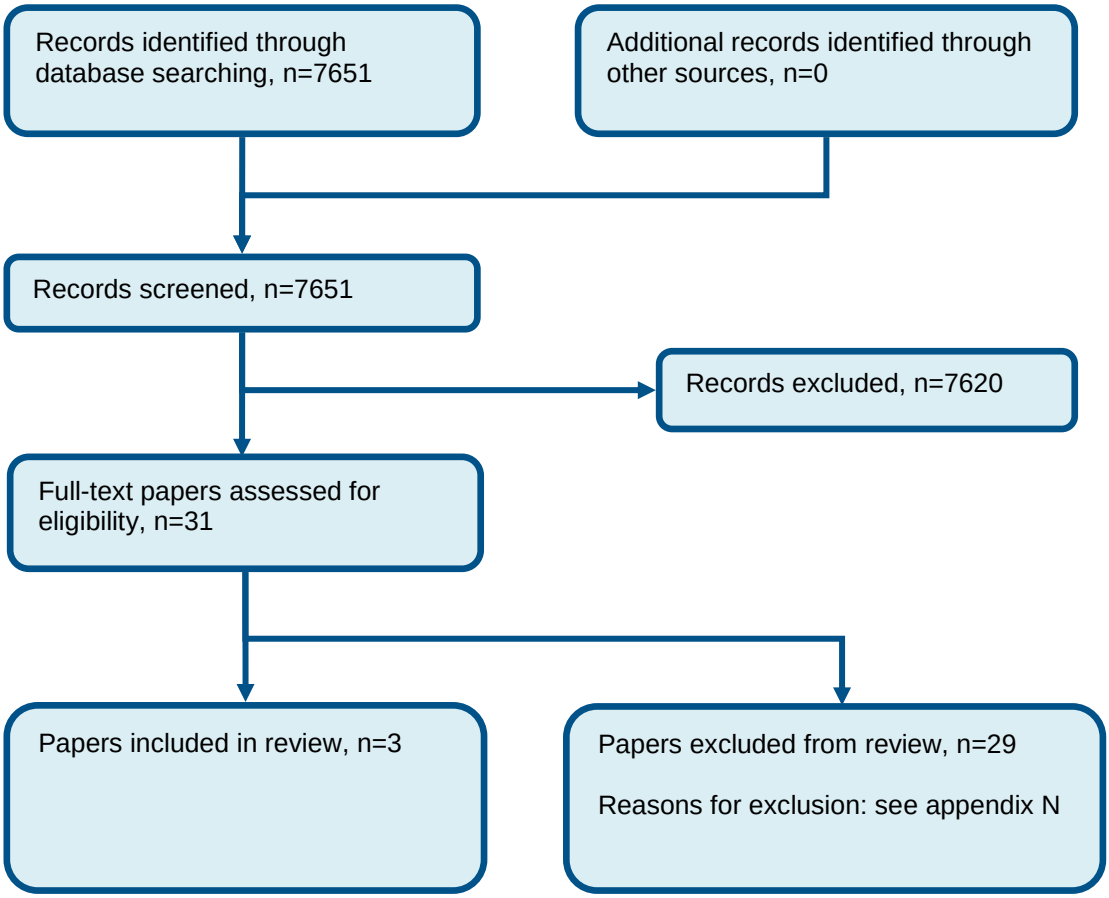
Appendix J: Clinical evidence selection

Figure 5: Flow chart of clinical study selection for the review of indications for investigation for diverticular disease.



Appendix K: Clinical evidence tables

Table 23: Clinical evidence tables

Reference	**Jung 2010[29]**
Study type and analysis	Cross-sectional; logistic regression analyses, adjusting for age and gender.
Number of participants and characteristics	Random samples, stratified by age and gender, of the residents of Olmsted County between 1988 and 1993. Subjects were classified as having IBS based on the symptoms recorded in a self-reported questionnaire. The diagnosis of diverticular disease was established by using any positive colon test among colonoscopy, flexible sigmoidoscopy, abdomen computed tomography (CT) scan and/or CT colonography, or barium enema. Total cohort = 1712 People with IBS n = 223 Mean age (SD) 62 (±12) years (range of 33–93 years) Gender (male/female) 45%/55%
Prognostic variable	Presence of IBS.
Confounders/ Stratification strategy	Adjusting for age and gender
Outcomes and effect sizes	Cases with diverticular disease Adjusted OR: 1.7 (95% CI 1.2 to 2.4) for IBS versus no IBS
Comments	Risk of bias: very high – study participation; study attrition.

Reference	**Lee 2012[34]**

Reference	Lee 2012[34]
Study type and analysis	Case-control; prospective analysis with matched (age and gender) control group
Number of participants and characteristics	Subjects undergoing CT colonography between April 2002 and April 2008 at the Samsung Medical Centre, Seoul were included. Subjects were divided into two groups: those with proven colorectal cancer (case group) and those with no colorectal cancer (control group) matched for age and gender. Subjects with previous polypectomy within 5 years; previous colonic resection for any reason; past or current diagnosis of inflammatory bowel disease; familial adenomatous polyposis; foreign patients; and metastatic colon cancer were excluded. Case group n= 302 Control group n=302 Mean age (range) Case: 56.9 years (28-85) Control: 56.8 (20-88) Gender (male) Case: 54.6% Control: 54.6%
Prognostic variable	Presence of colorectal cancer.
Confounders/ Stratification strategy	Age Gender
Outcomes and effect sizes	Cases with diverticulosis OR 0.78 (95% CI 0.54 to 1.11) for cancer versus no cancer
Comments	Risk of bias: very high – study participation.

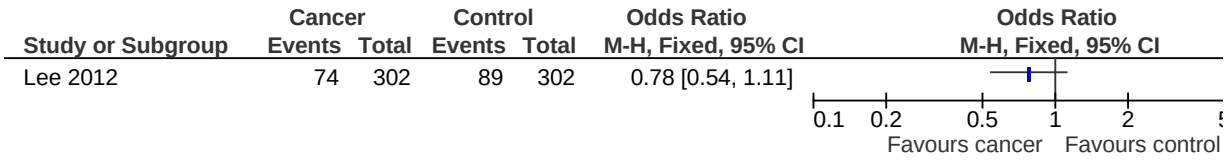
Reference	Sirinthornpunya 2014[51]
Study type and analysis	Cross-sectional; retrospective analysis with control group

Reference	Sirinthornpunya 2014[51]
Number of participants and characteristics	Patients ages 18 and over with clinical physical examination compatible with IBS. Control group were patients aged 18 and over who received colonoscopy for various indications. Exclusion criteria included patients with bowel obstruction, massive colon bleeding, colon perforation, inflammatory mass known colon or rectal cancer and patients with contraindication for colonoscopy. IBS patients, defined by Rome III criteria, and control group patients were enrolled. Case group n=75 Control group n=75 Mean age (SD) Case: 54.07 years (13.03) Control: 60.48 (12.09) Gender (female/male) Case: 46/29 Control: 40/35 BMI (SD) Case: 23.98 kg/m^2 (4.70) Control: 23.48 kg/m^2 (4.15)
Prognostic variable	Presence of IBS.
Confounders/ Stratification strategy	No difference was found in age, sex and BMI between the IBS and the control groups (p>0.05)
Outcomes and effect sizes	Cases with diverticular disease OR 2.64 (95% CI 1.07 to 6.54) for IBS versus no IBS
Comments	Risk of bias: very high – study participation; study confounding; statistical analysis.

Appendix L:Forest plots

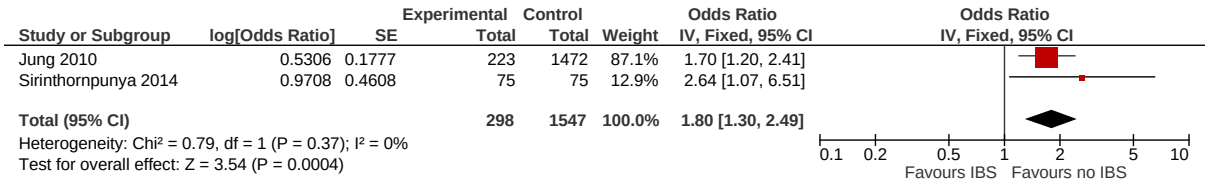
L.1 Colorectal cancer

Figure 6: Colorectal cancer versus no cancer in the event of diverticulosis



L.2 IBS

Figure 7: IBS versus no IBS in the event of diverticular disease



Appendix M: GRADE tables

Table 24: Clinical evidence profile: Colorectal cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colorectal cancer	Control	Relative (95% CI)	Absolute		
Diverticulosis												
1	case-series	serious[1]	no serious inconsistency	serious indirectness[2]	serious[3]	none	74/302 (24.5%)	29.5%	OR 0.78 (0.54 to 1.11)	49 fewer per 1000 (from 111 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment as the study outcome was Diverticulosis
[3] Imprecision was considered serious as the confidence interval crossed the line of null effect.

Table 25: Clinical evidence profile: IBS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IBS	Control	Relative (95% CI)	Absolute		
Diverticular disease												
2	cross-sectional	very serious[1]	no serious inconsistency	no serious indirectness	none	none	132/298 (24%)	1547	OR 1.80 (1.3 to 2.49)	Pooled result as OR	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Appendix N: Excluded studies

N.1 Excluded clinical studies

Table 26: Studies excluded from the clinical review

Reference	Reason for exclusion
Alexandersson 2014[2]	Excluded due to inappropriate population; no relevant outcome
Ambrosetti 1992[4]	Excluded due to inappropriate population; analysis
Andeweg 2013[5]	Excluded due to inappropriate study design
Bielecki 2002[7]	Excluded due to inappropriate population; no relevant outcome
Binda 2012[8]	Excluded due to inappropriate population
Carpenter 1972[11]	Excluded due to inappropriate study design
Cazacu 1997[12]	Excluded due to inappropriate analysis; study outcomes
Chang 2016[14]	Excluded due to inappropriate comparison
Del Rio 2014[16]	Excluded due to inappropriate comparison
Foster 1978[17]	Excluded due to inappropriate comparison
Granlund 2011[18]	Excluded due to inappropriate population; no relevant outcome
Gryspeerdt 2012[19]	Excluded due to inappropriate comparison
Havia 1971[20]	Excluded due to inappropriate study design; analysis
Huang 2014[22]	Excluded due to inappropriate population; no relevant outcome
Jung 2014[30]	Excluded due to inappropriate population; no relevant outcome
Maconi 2017[36]	Excluded due to no relevant outcome
Meeson 2009[37]	Excluded due to inappropriate comparison
Meyer 2015[38]	Excluded due to inappropriate population; no relevant outcome
Morini 1988[39]	Excluded due to inappropriate population; no relevant outcome
Mounce 2017[40]	Excluded due to inappropriate comparison
Niikura 2012[45]	Excluded due to inappropriate comparison
Oistamo 2013[46]	Excluded due to inappropriate comparison
Otte 1986[47]	Excluded due to inappropriate study design; analysis
Sallinen 2014[49]	Excluded due to inappropriate population; no relevant outcome
Stefansson 2004[55]	Excluded due to inappropriate population; no relevant outcome
Stefansson 1995[54]	Excluded due to inappropriate population; no relevant outcome

Reference	Reason for exclusion
Sultan 2006[57]	Excluded due to inappropriate comparison
Tursi 2013[59]	Excluded due to inappropriate comparison
Wong 2016[61]	Excluded due to inappropriate analysis i.e. no multivariate analysis.

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