National Institute for Health and Care Excellence

Consultation

Diverticular Disease

A. Evidence review: Prevention of diverticular disease in patients with diverticulosis

NICE guideline

Intervention evidence review

June 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre

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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.Diverticulosis

1.1 Review question: What is the most clinically and cost-effective management strategy for the prevention of diverticular disease in patients with diverticulosis?

1.2 Introduction

Diverticulosis, the presence of colonic diverticulae unaccompanied by inflammation or resulting symptoms is extremely common. Diverticulosis does not, in itself, constitute a pathological condition, without the progression to diverticular disease. Many, perhaps even the majority, of patients with diverticulosis will never develop diverticular disease. However, knowing how to reduce the risk of developing diverticular disease is important for many patients with diverticulosis. Following an incidental finding of diverticulosis many patients will ask their clinicians for advice on how to prevent diverticular disease or its complications. This section considers the evidence that exists for the clinical and cost effectiveness of conservative measures to prevent diverticular disease in patients with diverticulosis.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with diverticulosis

Intervention	• Dietary advice
	  ○ Dietary fibre: soluble and insoluble
	  ○ Red meat
	  ○ Any dietary advice
	• Probiotics, prebiotics
	• Other conservative management
	  ○ Exercise
	  ○ Weight loss
	  ○ Smoking
	• Use of laxatives

Comparison	• Each other • No treatment • Placebo

Outcomes	Critical outcomes:
	• Progression of disease:
	  ○ Symptomatic diverticular disease
	  ○ Acute diverticulitis
	  ○ Complications (infections, abscesses, perforation, stricture, fistula)
	• Quality of life
	
	Important outcomes:
	• Side effects:
	  ○ Diarrhoea
	  ○ Bloating
	  ○ Abdominal pain
	• Mortality

Study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs.
	• If no RCT evidence is available, search for observational studies. Confounders for observational studies:
	  ○ Age
	  ○ Gender

1.4 Clinical evidence

1.4.1 Included studies

No studies were included in the review. See the study selection flow chart in appendix C.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No relevant health economic studies were identified.

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

1.5.3 Unit costs

The unit costs below were presented to the Committee, to aid consideration of cost effectiveness.

Table 2: UK costs of probiotics, prebiotics and laxatives

Drug	Assumed daily dose [BNF][(a)]	Cost per unit (£)	Cost per month (£)[(b)]	Source
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets	1 x 4.4g sachet [once daily]	£1.15	£34.86	BNF (NHS indicative price)
Laxatives				
Isphagula husk 3.5g effervescent granules sachets	2 x 3.5g sachets [5-10g once daily]	£0.09	£5.52	NHS Drug Tariff
Methylcellulose 500mg	2 x 500mg tablets once daily [3-6 x 500mg tablets twice daily]	£0.05	£2.89	NHS Drug Tariff
Sterculia 62% granules 7g sachets	2 x 7g sachets twice daily [1-2 sachets 1-2 times a day]	£0.11	£13.53	NHS Drug Tariff
Bisacodyl 5mg gastro-resistant tablets	2 x 5mg tablets [5-10mg once daily increased if necessary up to 20mg once daily]	£0.21	£12.66	NHS Drug Tariff
Sodium picosulfate 5mg/5ml oral solution	2 x 5mg/ml solutions [5-10mg once daily]	£0.12	£7.20	NHS Drug Tariff
Senna 7.5mg tablets	2 x 7.5mg tablets [7.5-15mg daily (maximum dose 30 mg daily)]	£0.03	£1.67	NHS Drug Tariff
Lactulose 3.1g-3.7g/5ml oral solution	6 x 3.1g-3.7g/5ml oral solution [Initially 15ml twice daily, adjusted according to	£0.02	£4.13	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
	response]			
Macrogol 3350 oral powder 8.5g sachets	2 x 8.5g sachets [2 sachets once daily usually for up to 2 weeks]	£0.14	£3.89[c]	NHS Drug Tariff
Docusate sodium 100mg capsules (by mouth)	5 x 100g capsules [Up to 500mg daily in divided doses, adjusted according to response]	£0.07	£10.60	NHS Drug Tariff
Glycerol (by rectum) 4g suppositories	1 suppository [1 x 4g suppository, as required]	£0.10	£2.94	NHS Drug Tariff
Micralax (sodium citrate 90mg/ml) 5ml micro-enema	1 enema [1 enema per dose]	£0.41	£12.35	British National Formulary
Arachis oil 130ml enema	1 x 130ml enema [130ml, as required]	£47.50	£95[d]	NHS Drug Tariff

Sources: NHS Drug Tariff, February 2018; British National Formulary
(a) Dosages for adults, British National Formulary
(b) Depending on the number of units taken
(c) Cost per 14 days; not per month
(d) Cost per 2 days; not per month

Table 3: Example UK costs to people with diverticulosis for items not prescribed on the NHS

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets (non-prescribed)	1 x 4.4g sachet daily	£2.35	£71.47	Retail price from stockist[d]
Vivomixx (450 billion live bacteria per sachet) 4.4g sachets	1 x 4.4g sachet daily	£1.48	£45.02	Retail price from stockist[d]
Lactobacillus casei: Probio 10 (containing *L. casei* $5x10^7$ viable cells, among 10 different species of micro-organisms)	1 capsule daily	£0.08	£2.53	Not available in BNF; Retail price from stockist[e]
Symprove™	1ml/kg	£0.03/ml	£75.14[c]	Not available in BNF; Retail price from stockist[f]

Sources: Amazon.co.uk, Holland and Barrett, shop.symprove.com
(a) Dosages for adults
(b) Depending on the number of units taken
(c) Cost exclusive of VAT for a weight of 75kg, calculated from the average BMI (BMI 27.7) reported in Kvasnovsky 2017[9]
(d) Retail price obtained from Amazon.co.uk
(e) Retail price obtained from Holland and Barrett
(f) Retail price obtained from shop.symprove.com

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant clinical evidence was identified for this review question.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 Recommendations

Management and advice

A1. Tell people with diverticulosis that the condition is asymptomatic and no specific treatments are needed.

A2. Advise people to eat a healthy, balanced diet including whole grains, fruit and vegetables. Tell them that:

- there is no need to avoid seeds, nuts or fruit skins
- if they have constipation and a low-fibre diet, increasing their fibre intake gradually may minimise flatulence and bloating.

A3. Advise people to drink adequate fluid if they are increasing their fibre intake, especially if there is a risk of dehydration.

A4. Consider bulk-forming laxatives for people with constipation.

A5. Tell people about the benefits of exercise, and weight loss if they are overweight or obese, in reducing the risk of developing acute diverticulitis and symptomatic disease.

1.7.1 Research recommendations

RR1. What are the risk factors for diverticulosis progressing to diverticular disease in people with known diverticulosis?

RR2. What is the most clinically and cost-effective conservative management for preventing diverticular disease in people with diverticulosis?

See also the rationale in appendix I.

1.8 Rationale and impact

1.8.1 Why the committee made recommendations

Diverticulosis is asymptomatic and there are no specific treatments for it. The committee therefore considered making a recommendation about lifestyle and dietary advice to address the common questions asked by newly diagnosed patients about these factors to prevent progression of the disease. However, although some evidence was found on the management of diverticulosis, it did not meet the criteria for including in the review on what is the most clinically and cost-effective management strategy for preventing diverticular disease in patients with diverticulosis diverticulosis (see H1: Excluded clinical studies for the exclusion reasons). The committee were aware of evidence (which did not meet the review criteria) that vigorous exercise was associated with a reduction in risk of developing acute diverticulitis. Increased body mass index was also associated with an increased risk of symptomatic disease. In the absence of evidence that could be used to draft

recommendations, formal consensus methods and the knowledge and experience of the committee were used instead i.e. Delphi survey conducted (see Chapter R for more details). The recommendations should be straightforward to implement and may reduce the possibility of developing diverticular disease.

In light of the lack of evidence on this topic, and the need to know what factors might increase the risk of diverticulosis progressing to diverticular disease, the committee considered this an important area for research. It made research recommendations on risk factors for diverticular disease and on conservative management for preventing diverticular disease.

1.8.2 Impact of the recommendations on practice

The recommendation reflects current practice.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The Committee identified quality of life, and progression of disease into symptomatic diverticular disease, acute diverticulitis, or complications (infections, abscesses, perforation, stricture, and fistula) as the critical outcomes. The following outcomes were identified as important for management of diverticulosis; mortality, and side effects of probiotics and laxatives: diarrhoea, bloating, abdominal pain.

Mortality was considered an important rather than critical outcome as the committee acknowledged any mortality reported would unlikely be a result of diverticulosis.

No relevant published clinical studies were identified; therefore no evidence was available for any of these outcomes.

1.9.1.2 The quality of the evidence

No relevant clinical studies were identified for this review.

1.9.1.3 Benefits and harms

No relevant clinical studies were identified for this review. However, the Committee felt that a research recommendation in this area was warranted. Further research in this area could inform treatment so that people with diverticulosis receive the right care to prevent the development of disease, and the subsequent impact of health and wellbeing.

1.9.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of strategies to prevent disease progression in people with diverticulosis. In the absence of relevant economic evaluations, the committee considered the unit costs of laxatives and probiotics.

The committee chose to recommend that research be conducted on the clinical and cost effectiveness of management strategies for the prevention of diverticular disease in people with diverticulosis.

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 panel recommended dietary

and lifestyle advice and consideration of bulk-forming laxatives. The cost-effectiveness of laxatives in this context is not known. However, the costs are relatively small and the recommendations do not represent a move away from current practice.

1.9.3 Other factors the committee took into account

The committee appreciated the difficulty in identifying a population of people with diverticulosis and reiterated the large number of people who will be unaware of their disease in the absence of symptoms. Recent cross-sectional studies have reported that up to 40% of people aged 65-69 years may have diverticulosis and 55% of these had no history of abdominal pain in the last 3 months (Jarbrink-Sehgal, Clini Gas & hep Vol 14, 12 2016).

The committee noted that people with diverticulosis are asymptomatic (the findings are found incidentally during an investigation for another reason) and no specific treatments are indicated. The committee acknowledged that current practice for the treatment of adults with diverticulosis to prevent diverticular disease is to recommend a high-fibre diet and improved lifestyle factors including reduced alcohol intake, smoking cessation and exercise. The committee were aware of evidence from large observational reporting that vigorous exercise was associated with a reduction in risk of developing acute diverticulitis. Increased body mass index was also associated with an increased risk of symptomatic disease. Often bulk-forming laxatives are effective as they help to soften the stool and can also help solidify loose stools. The aim of these is to improve general wellbeing and an understanding of gut health; however, these recommendations are supported by evidence from observational studies that did not meet the review protocol criteria. Statements were therefore included in the Delphi survey and formed the basis of recommendations.

The statements on eating a diet that contains whole grains, fruit and vegetables, bulk forming laxatives, weight loss and exercise and routine follow-up reached consensus in the first round. The statement on drinking adequate fluid was modified by the committee after round one to refer to when increasing fibre intake (Delphi respondents did not suggest any amendments). The statement ‘to reduce red meat intake’ was removed after round one as Delphi respondents indicated there is no evidence to support it and neither the Delphi respondents nor the committee could suggest any amendments. Responses to the statement on increasing fibre intake indicated that there is no evidence to support this statement or that it may make symptoms worse for some people. The statement was modified by the committee to make it specific to people with constipation and it reached consensus in the second round. The reference to consuming 30g of fibre was removed as Delphi respondents noted, and the committee agreed, that there was no evidence for this and people would not know how to reach this target. The corresponding statements referring to a high fibre diet were removed. A recommendation on routine follow up reached consensus in the first round.

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Appendices

Appendix A: Review protocols

Table 4: Review protocol: Prevention of diverticular disease in patients with diverticulosis

Field	Content
Review question	What is the most clinically and cost-effective management strategy for the prevention of diverticular disease in patients with diverticulosis?
Type of review question	Intervention 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 find the most effective management for the prevention of diverticular disease in patients with diverticulosis. Diverticulosis is defined as structural abnormality with no symptoms, and it is usually accidentally found during diagnostic tests for other diseases. So the main aim of managing patients with diverticulosis is prevention of disease progression to diverticular disease.
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with diverticulosis (including people with asymptomatic or uncomplicated diverticular disease)

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Dietary advice
	  ○ Dietary fibre: soluble and insoluble
	  ○ Red meat
	  ○ Any dietary advice
	• Probiotics, prebiotics
	• Other conservative management
	  ○ Exercise
	  ○ Weight loss
	  ○ Smoking
	• Use of laxatives

Eligibility criteria – comparator(s) / control or reference (gold) standard	• Each other • No treatment • Placebo

Outcomes and prioritisation	Critical outcomes:
	• Progression of disease:
	  ○ Symptomatic diverticular disease
	  ○ Acute diverticulitis
	  ○ Complications (infections, abscesses, perforation, stricture, fistula)
	• Quality of life
	
	Important outcomes:
	• Side effects of probiotics and laxatives: diarrhoea, bloating, abdominal pain
	• Mortality

Eligibility criteria – study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs.
	• If no RCT evidence is available, search for observational studies.
	Confounders for observational studies:
	  ○ Age
	  ○ Gender

Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger • Primary prevention of diverticulosis
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 • age (<50 years and >50 years)
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)	• 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.
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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 5: 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).[12] **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.

B1. 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 6: 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 7: 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 8: 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 9: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B2. 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 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions

Database	Dates searched	Search filter used
		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

1 **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.	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)

1 **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.	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.

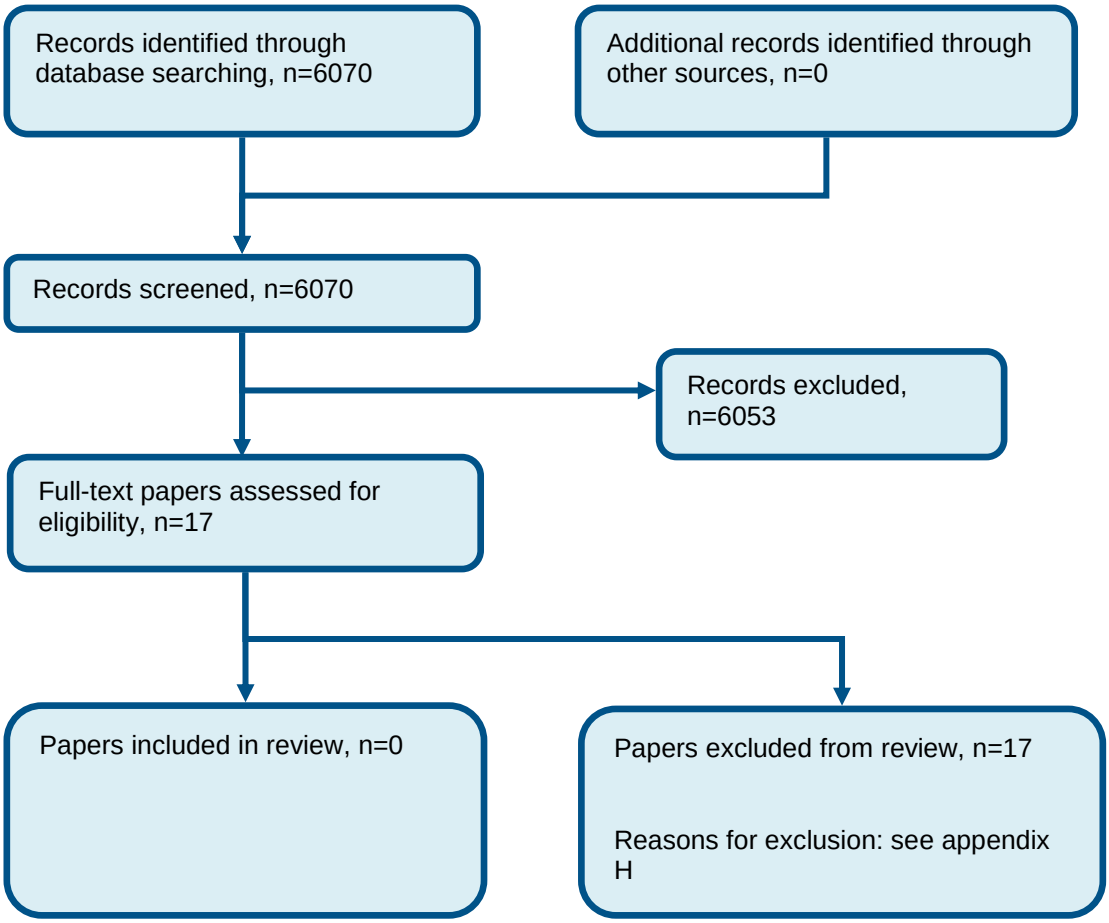
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* 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 13: 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 management of diverticulosis



Appendix D: Clinical evidence tables

No evidence was identified.

Appendix E: Forest plots

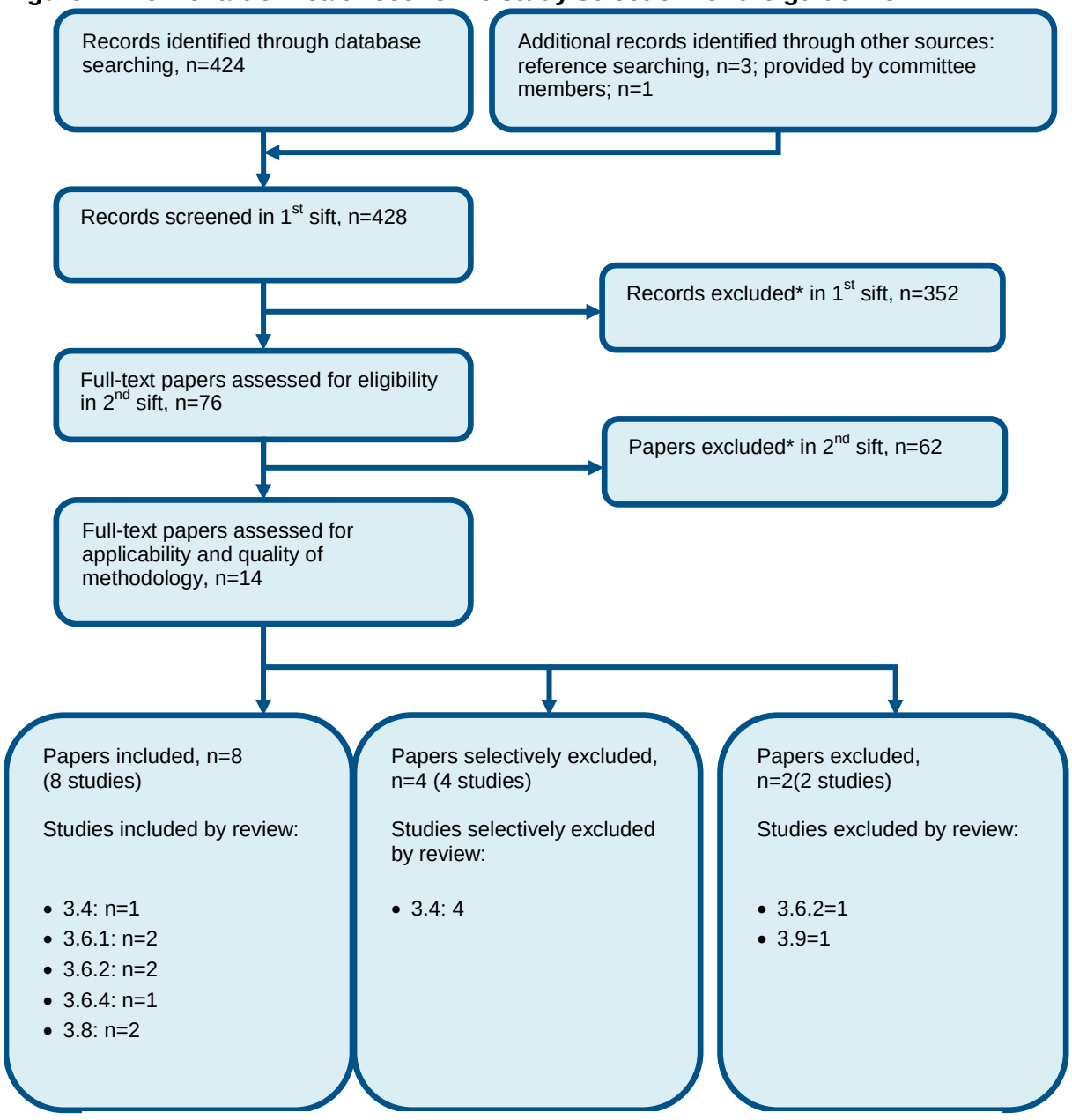
No evidence was identified.

Appendix F: GRADE tables

No evidence was identified.

Appendix G: Health economic evidence selection

Figure 2: 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

H1: Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Banasiewicz 2012[2]	Abstract only
Banasiewicz 2017[1]	Incorrect interventions
Correnti 1983[3]	Incorrect interventions
Crowe 2011[4]	Not guideline condition
Darnis 1980[5]	Not in English
Eglash 2006[6]	Literature review - references checked
Galeone 1987[7]	Not in English
Krokowicz 2014[8]	Not review population. Incorrect interventions
Lin 2000[10]	Incorrect study design. Inappropriate comparison. Not guideline condition
Mahmood 2018[11]	Incorrect study design
Nishida 2016[13]	Abstract only
Paszkowski 2016[14]	Abstract only
Peery 2012[15]	Not guideline condition
Strate 2008[17]	Not guideline condition
Strate 2017[16]	Not review population
Tarleton 2011[18]	Literature review - references checked
Thalheimer 2012[19]	Not in English

H2: Excluded health economic studies

None.

Appendix I: Research recommendations

I1: Prevention of diverticular disease

Research question: What are the risk factors for diverticulosis progressing to diverticular disease in people with known diverticulosis?

Why this is important:

A research recommendation could inform treatment to prevent the development of disease, and the subsequent impact of health and wellbeing. The committee acknowledged that the current practice of treatment for patients with diverticulosis in the prevention of diverticular disease is to recommend a high fibre diet and improved lifestyle factors, including reduced alcohol intake, smoking cessation and exercise. All are based on the knowledge of improved general wellbeing and an understanding of improved gut health but are not supported by evidence in a population of people with diverticulosis. The committee also highlighted the potential importance for people with diverticulosis of assessing the risk of developing symptomatic diverticular disease for subsequent assessment and treatment decisions. Such information may inform the focus of therapy for people who are diagnosed with diverticulosis but may also elucidate the extent to which interventions to prevent diverticular disease are justified.

Table 15: Criteria for selecting high-priority research recommendations

PICO question	**Population:** Adults aged 18 years and over with a diagnosis of diverticulosis/diverticular disease who are registered on the Clinical Research Database. **Intervention/comparison:** A comparison between those patients who have a diagnosis of diverticular disease matched to those who have a diagnosis of diverticulosis only. A retrospective study comparing those patients with a diagnosis of diverticular disease and those with just a diagnosis of diverticulosis. The two populations will be matched for age, sex, postcode and possible risk factors including weight, smoking history, alcohol intake and exercise. **Outcomes:** The development of diverticular disease.
Importance to patients or the population	High quality research in this area would allow the identification of the risks for the development of diverticular disease in those patients with a diagnosis of diverticulosis.
Relevance to NICE guidance	Currently there is uncertainty about the risk factors for diverticular disease for patients with diverticulosis.
Relevance to the NHS	A research recommendation could inform treatment and advice to prevent the development of disease, and the subsequent impact of health and wellbeing.
National priorities	
Current evidence base	There are no population studies examining the risk factors for the development of diverticular disease.
Equality	Patients of Asian origin may develop right sided diverticular disease and so present differently with right sided abdominal pain. These patients should be identified, and sub-group analysis performed.
Study design	Retrospective study.
Feasibility	This study should be straightforward as the database is well established and it is routinely used in this type of research.
Other comments	None.

Importance	High – Diverticulosis is a common condition in the older population. The development of diverticular disease has a significant impact on the health and well-being of the induvial as well as significant costs to the NHS.

I2: Prevention of diverticular disease

Research question: What is the most clinically and cost-effective conservative management for preventing diverticular disease in people with diverticulosis?

Why this is important:

Further prospective controlled trials are needed to establish whether dietary fire supplementation is beneficial in the prevention of diverticulitis in patient with established diverticulosis. Since a vegetarian diet may be protective against the development of diverticular disease, studies are needed to investigate whether such a diet would be effective in preventing recurrent diverticular disease in people with diverticulosis.

Further research is needed to establish whether meat eating is independently associated with an increased risk of development of diverticular disease. Further prospective studies are also needed to investigate whether dietary fibre intake has an independent effect on diverticular disease over and above a vegetarian diet, and to establish whether soluble fibre is more protective than non-soluble fibre.

Table 16: Criteria for selecting high-priority research recommendations:

PICO question	**Population**: Adults 18 years and over with a diagnosis of diverticulosis/diverticular disease **Intervention/comparison:** *Study 1:* • Vegetarian diet • Diet including meat intake *Study 2:* • High fibre diet • Moderate fibre diet • Low fibre diet **Outcomes:** • The development of diverticular disease. • Groups should be matched for factors including age, weight, exercise and smoking history.
Importance to patients or the population	High quality research in this area would allow the identification of interventions that will decrease the probability of developing diverticular disease in those people with a diagnosis of diverticulosis.
Relevance to NICE guidance	Currently there is uncertainty about what interventions reduce the risk of developing diverticular disease in people with diverticulosis.
Relevance to the NHS	A research recommendation could inform treatment and advice to prevent the development of disease, and the subsequent impact of health and wellbeing.
Current evidence base	There are only a small number of studies published mostly with a retrospective study design.

Equality	Patients of Asian origin may develop right sided diverticular disease and so present differently with right sided abdominal pain. These people should be identified, and sub-group analysis performed.
Study design	Randomised controlled trial.
Feasibility	A GP database is well established and could be used to identify people.
Other comments	None.
Importance	High – Diverticulosis is a common condition in the older population. The development of diverticular disease has a significant impact on the health and well-being of the induvial as well as significant costs to the NHS.

1