

Colorectal cancer (update)

[E2] Optimal management of low anterior resection syndrome

NICE guideline TBC

Evidence reviews

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Draft for Consultation

*These evidence reviews were developed by
the National Guideline Alliance hosted by the
Royal College of Obstetricians and
Gynaecologists*

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Contents

Contents	4
Optimal management of low anterior resection syndrome	7
Review question	7
Introduction	7
Summary of the protocol	7
Methods and process	8
Clinical evidence	8
Summary of clinical studies included in the evidence review	8
Quality assessment of clinical outcomes included in the evidence review	8
Economic evidence	8
Economic model	8
Evidence statements	9
The committee’s discussion of the evidence	9
References	10
Appendices	12
Appendix A – Review protocol	12
Review protocol for review question: What is the optimal management of low anterior resection syndrome?	12
Appendix B – Literature search strategies	16
Literature search strategies for review question: What is the optimal management of low anterior resection syndrome?	16
Appendix C – Clinical evidence study selection	18
Clinical study selection for: What is the optimal management of low anterior resection syndrome?	18
Appendix D – Clinical evidence tables	19
Clinical evidence tables for review question: What is the optimal management of low anterior resection syndrome?	19
Appendix E – Forest plots	20
Forest plots for review question: What is the optimal management of low anterior resection syndrome?	20
Appendix F – GRADE tables	21
GRADE tables for review question: What is the optimal management of low anterior resection syndrome?	21
Appendix G – Economic evidence study selection	22
Economic evidence study selection for review question: What is the optimal management of low anterior resection syndrome?	22
Appendix H – Economic evidence tables	23
Economic evidence tables for review question: What is the optimal management of low anterior resection syndrome?	23
Appendix I – Economic evidence profiles	24

Economic evidence profiles for review question: What is the optimal management of low anterior resection syndrome?	24
Appendix J – Economic analysis	25
Economic evidence analysis for review question: What is the optimal management of low anterior resection syndrome?	25
Appendix K – Excluded studies	26
Excluded clinical studies for review question: What is the optimal management of low anterior resection syndrome?.....	26
Appendix L – Research recommendations	30
Research recommendations for review question: What is the optimal management of low anterior resection syndrome?	30

1

1 Optimal management of low anterior 2 resection syndrome

3 This evidence review supports recommendations 1.6.2 to 1.6.4 and the research
4 recommendation on the effectiveness and safety of sacral nerve stimulation and trans-anal
5 irrigation compared to symptomatic treatment for people with major low anterior resection
6 syndrome.

7 Review question

8 What is the optimal management of low anterior resection syndrome?

9 Introduction

10 Low anterior resection syndrome (LARS) is a collection of symptoms that people who have
11 undergone a partial or total resection of the rectum might have. These symptoms include, for
12 example, faecal incontinence or leakage, frequency or urgency of stools, loose stools,
13 incomplete bowel movement, or tenesmus. These symptoms can have a considerable
14 negative impact on quality of life and daily functioning. A recent meta-analysis estimated the
15 prevalence of major LARS after sphincter-preserving rectal surgery to be around 40%
16 (Croese 2018). Different interventions have been suggested to treat or alleviate the
17 symptoms of LARS. The aim of this review is to find out which interventions are most
18 effective in improving quality of life and symptoms in people with LARS.

19 Summary of the protocol

20 Please see Table 1 for a summary of the population, intervention, comparison and outcomes
21 (PICO) characteristics of this review.

22 **Table 1: Summary of the protocol (PICO table)**

Population	Adults who have undergone treatment for rectal cancer with low anterior resection syndrome
Intervention	<ul style="list-style-type: none">• Dietary management• Bio-feedback• Pharmacotherapy:<ul style="list-style-type: none">○ Laxatives○ Anti-diarrhoeal agents○ Bulking agents○ Anti-spasmodic agents• Sacral nerve stimulation• Physiotherapy• Irrigation (wash out)• Stoma
Comparison	<ul style="list-style-type: none">• Individual interventions or combinations of interventions compared to each other• No treatment/active monitoring/placebo
Outcomes	Critical <ul style="list-style-type: none">• Quality of life<ul style="list-style-type: none">○ Overall○ Bowel function• Change in LARS score

1 *LARS: low anterior resection syndrome*

2 For further details see the review protocol in appendix A.

3 **Methods and process**

4 This evidence review was developed using the methods and process described in
5 [Developing NICE guidelines: the manual 2014](#). Methods specific to this review question are
6 described in the review protocol in appendix A.

7 Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy
8 until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to
9 NICE's 2018 [conflicts of interest policy](#). Those interests declared until April 2018 were
10 reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

11 **Clinical evidence**

12 **Included studies**

13 A systematic review of the clinical literature was conducted but no studies were identified
14 which were applicable to this review question.

15 See the literature search strategy in appendix B and study selection flow chart in appendix C.

16 **Excluded studies**

17 Studies not included in this review with reasons for their exclusions are provided in appendix
18 K.

19 **Summary of clinical studies included in the evidence review**

20 No studies were identified which were applicable to this review question (and so there are no
21 evidence tables in Appendix D). No meta-analysis was undertaken for this review (and so
22 there are no forest plots in Appendix E).

23 **Quality assessment of clinical outcomes included in the evidence review**

24 No studies were identified which were applicable to this review question.

25 **Economic evidence**

26 **Included studies**

27 A systematic review of the economic literature was conducted but no economic studies were
28 identified which were applicable to this review question.

29 **Excluded studies**

30 A global search of economic evidence was undertaken for all review questions in this
31 guideline. See Supplement 2 for further information.

32 **Economic model**

33 No economic modelling was undertaken for this review because the committee agreed that
34 other topics were higher priorities for economic evaluation.

1 Evidence statements

2 Clinical evidence statements

3 No evidence was identified which was applicable to this review question.

4 Economic evidence statements

5 No economic evidence was identified which was applicable to this review question.

6 The committee's discussion of the evidence

7 Interpreting the evidence

8 *The outcomes that matter most*

9 Overall quality of life, quality of life in terms of bowel function and LARS score were
10 considered to be critical outcomes for decision making as effectiveness of any intervention
11 for LARS would depend on the person's experience of LARS and its impact on their quality of
12 life. LARS score is used to assess if a person has LARS and the severity of LARS with 3
13 categories "no LARS", "minor LARS" and "major LARS". LARS score has been shown to
14 inversely correlate with quality of life scales, that is, the lower the LARS score the higher the
15 quality of life score (Emmertsen 2012, Juul 2015).

16 *The quality of the evidence*

17 No evidence was identified which was applicable to this review question.

18 *Benefits and harms*

19 LARS is a common problem among people who have undergone sphincter-preserving
20 surgery for rectal cancer but it is often unrecognised and untreated. LARS can have a
21 significant negative effect on a person's physical, psychological, social and sexual quality of
22 life. The committee noted that in addition to sphincter-preserving surgery, local radiotherapy
23 can sometimes cause functional problems or exacerbate the symptoms of LARS.

24 In current practice, a formal assessment of LARS is usually not done and the committee
25 discussed how patients report they are often not asked about their symptoms and their LARS
26 is often not recognised. If not specifically asked, patients often do not report their symptoms
27 because they might assume it is a normal consequence of their disease and treatment.
28 Furthermore, follow-up is usually done in primary care where there might not be specialised
29 knowledge about colorectal surgery and its possible consequences.

30 The committee agreed that it is important that people who may undergo sphincter-preserving
31 surgery for rectal cancer are made aware of the symptoms of LARS and given advice to seek
32 help from primary care if they experience them.

33 It is also important that people who have symptoms of LARS are formally assessed by using
34 a validated tool, such as the LARS score. The LARS score is measured by a validated, self-
35 administered questionnaire which is publicly available, simple to administer and score
36 (Emmertsen 2012, Juul 2015). The scale is from 0 to 42 points with 0 to 20 points indicating
37 that the patient does not have LARS, 21 to 29 points indicating minor LARS, and 30 to 42
38 points indicating major LARS.

39 The committee discussed that there is often a latent period and the symptoms of LARS might
40 only appear later in which case the postoperative check might not be the appropriate time
41 point to assess LARS, therefore, it is important that the GPs are knowledgeable about LARS
42 and LARS score.

1 No randomised, comparative evidence was identified on the different interventions to treat
2 LARS, therefore, the committee was unable to recommend a particular treatment but instead,
3 based on their expertise, recommended that conservative treatments for bowel dysfunction
4 should be offered in primary care. These treatments may include:

- 5 • dietary management
- 6 • laxatives
- 7 • bulking agents
- 8 • anti-diarrhoeal
- 9 • anti-spasmodic
- 10 • physiotherapy input.

11 If these treatments are unsuccessful, a referral should be made to secondary care where
12 other options could be discussed. Sometimes physiotherapy would also require a referral to
13 secondary care. Small single-arm studies or observational studies have suggested that
14 sacral nerve stimulation and trans-anal irrigation might be effective in treating LARS but
15 randomised trials are needed to investigate their effectiveness (Dulskas 2018). Therefore,
16 the committee decided to make a research recommendation on the effectiveness and safety
17 of sacral nerve stimulation and trans-anal irrigation compared to symptomatic treatment for
18 people with LARS. See appendix L for more details about the research recommendation.

19 **Cost effectiveness and resource use**

20 No economic evidence was identified that addressed this topic.

21 There may be some cost increase associated with assessing patients using the LARS score
22 as formal assessments are not usually carried out at present. However, since the test is
23 patient-administered it should not require too much GP time. It is also easy to score and so
24 training should not be required to use the test. Thus overall, the cost impact is not expected
25 to be significant.

26 While there may be some modest cost increases associated with the assessment, there
27 should also be clinical benefits associated with correctly identifying and managing patients
28 with LARS. These benefits would be expected to translate into QALY gains and it is therefore
29 likely that the assessments would be cost-effective in cost per QALY terms.

30 Regarding treatment for LARS, the recommendation reflects current practice where most of
31 the conservative treatments are already offered in primary care and referral is done only
32 when those are not successful.

33 **References**

34 **Croese 2018**

35 Croese A, Lonie J, Trollope A, et al. (2018) A meta-analysis of the prevalence of Low
36 Anterior Resection Syndrome and systematic review of risk factors. *International Journal of*
37 *Surgery* 56: 234-41

38 **Dulskas 2018**

39 Dulskas A, Smolskas E, Kildusiene I et al. (2018) Treatment possibilities for low anterior
40 resection syndrome: a review of the literature. *International Journal of Colorectal Disease*
41 33(3): 251-60

42 **Emmertsen 2012**

- 1 Emmertsen KJ and Laurberg S (2012) Low anterior resection syndrome score: Development
- 2 and validation of a symptom-based scoring system for bowel dysfunction after low anterior
- 3 resection for rectal cancer. *Annals of Surgery* 255(5) :922-8
- 4 **Juul 2015**
- 5 Juul T, Battersby NJ, Christensen P, et al. (2015) Validation of the English translation of the
- 6 low anterior resection syndrome score. *Colorectal Diseases* 17(10) :908-16

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: What is the optimal management of 4 low anterior resection syndrome?

5 **Table 2: Review protocol for management of low anterior resection syndrome**

Field (based on PRISMA-P)	Content
Review question	What is the optimal management of low anterior resection syndrome?
Type of review question	Intervention
Objective of the review	Low anterior resection syndrome (LARS) is a collection of symptoms that people who have after undergone a partial or total resection of the rectum might have. These symptoms include for example frequency or urgency of stools, loose stools, incontinence or leakage, incomplete bowel movement, fragmented stools or tenesmus. These symptoms can have a huge negative impact in quality of life and daily functioning. Therefore, it is important to find out what management options are most effective in improving quality of life for these people.
Eligibility criteria – population/disease/condition/issue/domain	Adults who have undergone treatment for rectal cancer with low anterior resection syndrome
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	<ul style="list-style-type: none"> • Dietary management • Bio-feedback • Pharmacotherapy: <ul style="list-style-type: none"> ○ Laxatives ○ Anti-diarrhoeal agents ○ Bulking agents ○ Anti-spasmodic agents • Sacral nerve stimulation • Physiotherapy • Irrigation (wash out) • Stoma
Eligibility criteria – comparator(s)/control or reference (gold) standard	<ul style="list-style-type: none"> • Individual interventions or combinations of interventions compared to each other • No treatment/active monitoring/placebo
Outcomes and prioritisation	<p>Critical:</p> <ul style="list-style-type: none"> • Quality of life measured using validated scales only (MID: from literature, see list below) • Overall • Bowel function • Change in LARS score (MID: 5) <ul style="list-style-type: none"> • Quality of life MIDs from the literature: <ul style="list-style-type: none"> • EORTC QLQ-C30: 5 points • EORTC QLQ-CR29: 5 points

Field (based on PRISMA-P)	Content
	<ul style="list-style-type: none"> • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points • FACT-G: 5 points • SF-12: > 3.77 for the mental component summary and > 3.29 for the physical component summary • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary
Eligibility criteria – study design	<ul style="list-style-type: none"> • Systematic reviews • RCTs • Comparative observational studies
Other inclusion exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • English-language • Published full texts • All settings will be considered that consider medications and treatments available in the UK • Studies published 2008 onwards <p>Only studies published 2008 onwards will be considered for this review question because the guideline committee considered that older studies would not be relevant since LARS was only defined in 2012.</p>
Proposed sensitivity/sub-group analysis, or meta-regression	<p>Subgroups to be analysed separately:</p> <ul style="list-style-type: none"> • Women who have had children (as pelvic floor muscles are expected to be weaker in women who have had children) • People who had radiotherapy • Partial versus total resection of the rectum <p>For non-randomised data, analysis should include multivariate analysis with at least the following variables:</p> <ul style="list-style-type: none"> • Sex
Selection process – duplicate screening/selection/analysis	<p>Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer.</p> <p>Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.</p>
Data management (software)	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p> <p>'GRADEpro' will be used to assess the quality of evidence for each outcome.</p> <p>NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.</p>

Field (based on PRISMA-P)	Content
Information sources – databases and dates	<p>Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase</p> <ul style="list-style-type: none"> • Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance, but download all results • Dates: from 2008
Identify if an update	Not an update
Author contacts	<p>https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA</p>
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 (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	<p>Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist:</p> <ul style="list-style-type: none"> • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies <p>The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE.</p> <p>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</p>
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	<p>Synthesis of data: Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed.</p> <p>Minimally important differences: For quality of life published MIDs from literature will be used (see outcomes section for more information).</p>

Field (based on PRISMA-P)	Content
	MID for LARS score was based on the judgement of the committee.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual . If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Confidence in cumulative evidence	For details 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 guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual . Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

1 CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic
2 Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions
3 questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer
4 Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research
5 and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC
6 QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
7 colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire
8 (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general);
9 GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health
10 Technology Assessment; LARS: low anterior resection syndrome; MID: minimal important difference;
11 NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and
12 Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analysis
13 Protocols; PROSPERO: International prospective register of systematic reviews; RCT: randomised
14 controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions;
15 ROBIS: a tool for assessing risk of bias in systematic reviews; SF-12: 12-Item Short Form Survey; SF-
16 36: 36-Item Short Form Survey

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: What is the optimal management 3 of low anterior resection syndrome?

4 Database: Embase/Medline

5 Last searched on: 12/02/2019

#	Search
1	exp Rectal Neoplasms/ use prmz
2	*rectum cancer/ or *rectum tumor/
3	2 use oomezd
4	((rectal or rectum) adj3 (cancer* or neoplas* or malignan* or tumo?* or carcinom* or adeno*)).ti,ab.
5	1 or 3 or 4
6	exp Postoperative Complications/ or exp Anastomosis, Surgical/ or exp Rectum/su [Surgery]
7	6 use prmz
8	exp postoperative complication/ or exp anastomosis/ or rectum anastomosis/ or rectum surgery/ or rectum anterior resection/ or rectum resection/
9	8 use oomezd
10	(low anterior resection syndrome or LARS or postoperative complication* or anastomosis).ti,ab.
11	7 or 9 or 10
12	5 and 11
13	exp Anal Canal/ or exp Fecal Incontinence/ or exp Constipation/ or exp "Quality of Life"/ or exp Defecation/ or exp "Recovery of Function"/ or exp Diarrhea/ or exp Anastomotic Leak/ or exp Intestinal Obstruction/ or exp Electric Stimulation Therapy/ or exp Diet/ or exp Biofeedback, Psychology/ or exp Physical Therapy Modalities/ or exp Therapeutic Irrigation/ or exp Surgical Stomas/ or exp Drug Therapy/ or exp Loperamide/ or exp Laxatives/ or exp Antidiarrheals/ or exp Dietary Fiber/ or exp Flatulence/
14	13 use prmz
15	exp feces incontinence/ or exp constipation/ or exp "quality of life"/ or exp defecation/ or exp convalescence/ or exp diarrhea/ or exp anastomosis leakage/ or exp intestine obstruction/ or exp electrotherapy/ or exp diet/ or exp biofeedback/ or exp physiotherapy/ or exp lavage/ or exp stoma/ or exp intestine function disorder/ or exp drug therapy/ or exp loperamide/ or exp laxative/ or exp antidiarrheal agent/ or exp dietary fiber/ or exp flatulence/ or exp anus sphincter/ or exp bulking agent/ or exp electrostimulation/ or exp sacral nerve stimulation/ or exp sexual function/ or exp urinary dysfunction/
16	15 use oomezd
17	(score* or scale* or (bowel adj (dysfunction* or function* or movement*)) or (functional adj (outcome* or result*)) or manag* or cope or leak* or anal canal or anal sphincter or diarrh?ea* or laxative* or bulking agent* or anti-spasmodic agent* or physiotherap* or biofeedback* or diet* or food* or meal* or drink* or fluid* or sacral nerve stimulation* or continen* or incontinen* or irrigat* or wash?out or lavage* or abdominal pain* or stoma* or stool* or cluster* or fecal or constipat* or gas or imodium or metacucil or fiber or survival pack* or urinary function* or sexual function* or counsel* or nerve damage or exercis* or muscle strength* or recover* or "quality of life").ti,ab.
18	14 or 16 or 17
19	12 and 18
20	limit 19 to english language
21	limit 20 to yr="2008 -Current"
22	from 21 keep 1-5000
23	from 21 keep 5001-8274
24	remove duplicates from 22
25	remove duplicates from 23
26	24 or 25
27	(conference abstract or letter).pt. or letter/ or editorial.pt. or note.pt. or case report/ or case study/ use oomezd
28	Letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/ use prmz
29	(letter or comment* or abstracts).ti.
30	or/27-29
31	randomized controlled trial/ use prmz
32	randomized controlled trial/ use oomezd
33	random*.ti,ab.
34	or/31-33
35	30 not 34
36	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ use prmz
37	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ use oomezd
38	(rat or rats or mouse or mice).ti.
39	35 or 36 or 37 or 38
40	26 not 39

#	Search
41	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
42	41 use prmz
43	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
44	43 use oomezd
45	or/42,44
46	epidemiologic studies/ or observational study/ or case control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/
47	46 use prmz
48	exp observational study/ or exp case control study/ or exp retrospective study/ or exp cohort analysis/ or exp longitudinal study/ or exp follow up/ or exp prospective study/ or exp cross-sectional study/
49	48 use oomezd
50	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys**)).ti.
51	47 or 49 or 50
52	45 or 51

1 Database: Cochrane Library

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Rectal Neoplasms] explode all trees
2	(rectal or rectum) near (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)
3	#1 or #2
4	MeSH descriptor: [Postoperative Complications] explode all trees
5	low anterior resection syndrome or LARS or postoperative complication* or anastomosis
6	#4 or #5
7	#3 and #6
8	MeSH descriptor: [Anal Canal] explode all trees
9	MeSH descriptor: [Fecal Incontinence] explode all trees
10	MeSH descriptor: [Constipation] explode all trees
11	MeSH descriptor: [Quality of Life] explode all trees
12	MeSH descriptor: [Defecation] explode all trees
13	MeSH descriptor: [Recovery of Function] explode all trees
14	MeSH descriptor: [Diarrhea] explode all trees
15	MeSH descriptor: [Anastomotic Leak] explode all trees
16	MeSH descriptor: [Intestinal Obstruction] explode all trees
17	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
18	MeSH descriptor: [Diet] explode all trees
19	MeSH descriptor: [Biofeedback, Psychology] explode all trees
20	MeSH descriptor: [Physical Therapy Modalities] explode all trees
21	MeSH descriptor: [Therapeutic Irrigation] explode all trees
22	MeSH descriptor: [Surgical Stomas] explode all trees
23	MeSH descriptor: [Drug Therapy] explode all trees
24	MeSH descriptor: [Loperamide] explode all trees
25	MeSH descriptor: [Laxatives] explode all trees
26	MeSH descriptor: [Antidiarrheals] explode all trees
27	MeSH descriptor: [Dietary Fiber] explode all trees
28	MeSH descriptor: [Flatulence] explode all trees
29	score* or scale* or (bowel near (dysfunction* or function* or movement*)) or (functional near (outcome* or result*)) or manag* or cope or leak* or anal canal or anal sphincter or diarrh?ea* or laxative* or bulking agent* or anti-spasmodic agent* or physiotherap* or biofeedback* or diet* or food* or meal* or drink* or fluid* or sacral nerve stimulation* or continen* or incontinen* or irrigat* or wash?out or lavage* or abdominal pain* or stoma* or stool* or cluster* or fecal or constipat* or gas or imodium or metamucil or fiber or survival pack* or urinary function* or sexual function* or counsel* or nerve damage or exercis* or muscle strength* or recover* or "quality of life"
30	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
31	#7 and #30 Publication Year from 2008 to 2018

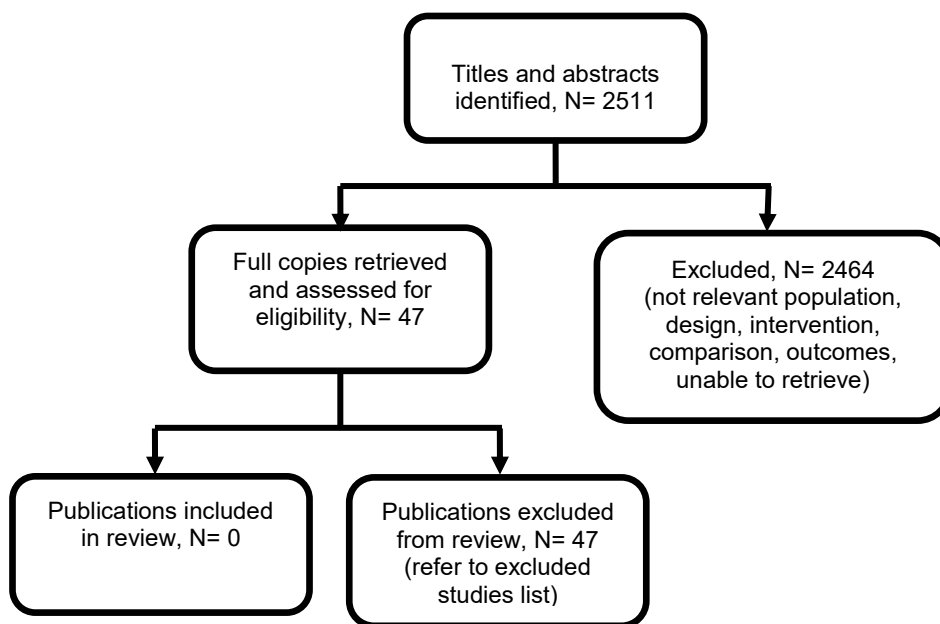
3

4

1 Appendix C – Clinical evidence study selection

2 Clinical study selection for: What is the optimal management of low anterior 3 resection syndrome?

Figure 1: Study selection flow chart



4

1 **Appendix D – Clinical evidence tables**

- 2 **Clinical evidence tables for review question: What is the optimal management of low**
- 3 **anterior resection syndrome?**
- 4 No clinical evidence was identified which was applicable to this review question.

1 **Appendix E – Forest plots**

2 **Forest plots for review question: What is the optimal management of low anterior** 3 **resection syndrome?**

4 No clinical evidence was identified which was applicable to this review question.

1 **Appendix F – GRADE tables**

- 2 **GRADE tables for review question: What is the optimal management of low anterior**
- 3 **resection syndrome?**
- 4 No clinical evidence was identified which was applicable to this review question.

1 **Appendix G – Economic evidence study selection**

2 **Economic evidence study selection for review question: What is the optimal** 3 **management of low anterior resection syndrome?**

4 A global search of economic evidence was undertaken for all review questions in this
5 guideline. See Supplement 2 for further information.

1 **Appendix H – Economic evidence tables**

- 2 **Economic evidence tables for review question: What is the optimal management of**
- 3 **low anterior resection syndrome?**
- 4 No economic evidence was identified which was applicable to this review question.

1 **Appendix I – Economic evidence profiles**

2 **Economic evidence profiles for review question: What is the optimal management of** 3 **low anterior resection syndrome?**

4 No economic evidence was identified which was applicable to this review question.

1 **Appendix J – Economic analysis**

2 **Economic evidence analysis for review question: What is the optimal** 3 **management of low anterior resection syndrome?**

4 No economic analysis was conducted for this review question.

5

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the optimal management of 3 low anterior resection syndrome?

4 Table 3: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Altomare, D. F., Picciariello, A., Ferrara, C., Digennaro, R., Ribas, Y., De Fazio, M., Short-term outcome of percutaneous tibial nerve stimulation for low anterior resection syndrome: results of a pilot study, <i>Colorectal Disease</i> , 19, 851-856, 2017	No comparison group.
Amos, M. L., Latham, D., Lillie, A. K., Farmer, M., "Development of a nurse led clinical treatment pathway for the management of patients that develop Low Anterior Resection Syndrome (LARS) post rectal cancer surgery" by Amos M, Latham D, Lillie AK (2016), <i>Colorectal Disease</i> , 19 (Supplement 4), 3, 2017	Conference abstract
Badic, B., Joumond, A., Thereaux, J., Gancel, C. H., Bail, J. P., Long-term functional and oncological results after sphincter-saving resection for rectal cancer - Cohort study, <i>International Journal Of Surgery</i> , 52, 1-6, 2018	Population not relevant.
Borstlap, W. A. A., Musters, G. D., Stassen, L. P. S., van Westreenen, H. L., Hess, D., van Dieren, S., Festen, S., van der Zaag, E. J., Tanis, P. J., Bemelman, W. A., Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study, <i>Surgical Endoscopy and Other Interventional Techniques</i> , 32, 315-327, 2018	Population not relevant.
Bryant, C. L., Lunniss, P. J., Knowles, C. H., Thaha, M. A., Chan, C. L., Anterior resection syndrome, <i>Lancet Oncology</i> , 13, e403-8, 2012	A narrative review about anterior resection syndrome. Possibly relevant referenced checked.
Bujko, K., Is adjuvant chemotherapy justified in rectal cancer patients after radiochemotherapy and radical resection?, <i>Nowotwory</i> , 68, 157-160, 2018	Population not relevant.
Cho, H., Kim, G., Yoo, R., Kye, B., Kim, H., The effect of biofeedback therapy during interval of temporary stoma on anorectal function: The interim report of randomized controlled study (NCT01661829), <i>Diseases of the Colon and Rectum</i> , 59 (5), e249, 2016	Conference abstract
Croese, A. D., Whiting, S., Vangaveti, V. N., Ho, Y. H., Using sacral nerve modulation to improve continence and quality of life in patients suffering from low anterior resection syndrome, <i>ANZ Journal of Surgery</i> , 88, E787-E791, 2018	Not randomised and does not present multivariate analysis
Cuicchi, D., Cipressi, C., Pinto, C., Lecce, F., De Raffele, E., Mirarchi, M., Ardizzoni, A., Cola, B., Percutaneous posterior tibial nerve stimulation versus medical therapy for the treatment of low anterior resection syndrome: Clinical and manometric short-term outcome of a randomized pilot trial, <i>Diseases of the Colon and Rectum</i> , 59 (5), e111, 2016	Conference abstract
De Miguel, M., Oteiza, F., Ciga, M. A., Armendariz, P., Marzo, J., Ortiz, H., Sacral nerve stimulation for the treatment of faecal incontinence following low anterior resection for rectal cancer, <i>Colorectal Disease</i> , 13, 72-77, 2011	No comparison group.
D'Hondt, M., Nuytens, F., Kinget, L., Decaestecker, M., Borgers, B., Parmentier, I., Sacral neurostimulation for low anterior	No comparison group.

resection syndrome after radical resection for rectal cancer: evaluation of treatment with the LARS score, <i>Techniques in Coloproctology</i> , 21, 301-307, 2017	
Didailler, R., Denost, Q., Loughlin, P., Chabrun, E., Ricard, J., Picard, F., Zerbib, F., Rullier, E., Antegrade Enema After Total Mesorectal Excision for Rectal Cancer: The Last Chance to Avoid Definitive Colostomy for Refractory Low Anterior Resection Syndrome and Fecal Incontinence, <i>Diseases of the Colon & Rectum</i> , 61, 667-672, 2018	Not comparative.
Dulskas, A., Smolskas, E., Kildusiene, I., Samalavicius, N. E., Treatment possibilities for low anterior resection syndrome: a review of the literature, <i>International Journal of Colorectal Disease</i> , 08, 08, 2018	A systematic review, no meta-analysis. Included studied checked individually for relevance.
Eftaiha, S. M., Balachandran, B., Marecik, S. J., Mellgren, A., Nordenstam, J., Melich, G., Prasad, L. M., Park, J. J., Sacral nerve stimulation can be an effective treatment for low anterior resection syndrome, <i>Colorectal Disease</i> , 19, 927-933, 2017	No comparison group.
Faulkner, G., Barrow, E., Ryder, S., Hill, J., The use of rectal irrigation in the management of low anterior resection syndrome (LARS), <i>Colorectal Disease</i> , 2), 91-92, 2014	Conference abstract
Gadan Does a Defunctioning Stoma Impair Anorectal Function after Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial, <i>Diseases of the Colon and Rectum</i> , 60, 800 806, 2017	Population not relevant.
Herman, R., Nowakowski, M., Transanal electrostimulation after intersphincteric rectum resection due to rectal cancer, <i>Annals of Oncology</i> , 5), v128, 2011	Conference abstract
Hou, X. T., Pang, D., Lu, Q., Yang, P., Jin, S. L., Bowel Dysfunction and Self-management for Bowel Symptoms After Sphincter-Preserving Surgery: A Cross-sectional Survey of Chinese Rectal Cancer Patients, <i>Cancer Nursing</i> , 40, E9-E16, 2017	No relevant interventions or outcomes.
Keane, C., Park, J., Oberg, S., Wedin, A., Bock, D., O'Grady, G., Bissett, I., Rosenberg, J., Angenete, E., Functional outcome in a randomised trial of early closure of temporary ileostomy after rectal resection for cancer (EASY trial), <i>Colorectal Disease</i> , 20 (Supplement 4), 3, 2018	Conference abstract
Kim, K. H., Yu, C. S., Yoon, Y. S., Yoon, S. N., Lim, S. B., Kim, J. C., Effectiveness of biofeedback therapy in the treatment of anterior resection syndrome after rectal cancer surgery, <i>Diseases of the Colon and Rectum</i> , 54, 1107-1113, 2011	No comparison group.
Klek, S., Pisarska, M., Milian-Ciesielska, K., Cegielnny, T., Choruz, R., Salowka, J., Szybinski, P., Pedziwiatr, M., Early closure of the protective ileostomy after rectal resection should become part of the enhanced recovery after surgery (ERAS) protocol: A randomized, prospective, two-center clinical trial, <i>Wideochirurgia I Inne Techniki Maloinwazyjne</i> , 13, 435-441, 2018	Population not relevant.
Koch, S. M., Rietveld, M. P., Govaert, B., van Gemert, W. G., Baeten, C. G., Retrograde colonic irrigation for faecal incontinence after low anterior resection, <i>Int J Colorectal Dis</i> , 24, 1019-22, 2009	No comparison group.
Laforest, A, Bretagnol, F, Mouazan, As, Maggiori, L, Ferron, M, Panis, Y, Functional disorders after rectal cancer resection: does a rehabilitation programme improve anal continence and quality of life?, <i>Colorectal Disease</i> , 14, 1231-1237, 2012	Population not relevant. This is a matched cohort study among people who had sphincter-saving surgery for rectal cancer,

	inclusion criteria does not include LARS or functional symptoms.
Liang, Z., Ding, W., Chen, W., Wang, Z., Du, P., Cui, L., Therapeutic Evaluation of Biofeedback Therapy in the Treatment of Anterior Resection Syndrome After Sphincter-Saving Surgery for Rectal Cancer, <i>Clinical Colorectal Cancer</i> , 15, e101-e107, 2016	No relevant comparison group.
Lin, Y. H., Chen, H. P., Liu, K. W., Fecal Incontinence and Quality of Life in Adults With Rectal Cancer After Lower Anterior Resection, <i>Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society</i> , 42, 395-400, 2015	No relevant interventions. The study evaluates fecal incontinence and quality of life of people who underwent low anterior resection for rectal cancer.
Lindgren, R, Hallböök, O, Rutegård, J, Sjö Dahl, R, Matthiessen, P, Does a defunctioning stoma affect anorectal function after low rectal resection? Results of a randomized multicenter trial, <i>Diseases of the Colon and Rectum</i> , 54, 747-752, 2011	No relevant intervention.
Liu, C. H., Chen, C. H., Lee, J. C., Rehabilitation exercise on the quality of life in anal sphincter-preserving surgery, <i>Hepato-Gastroenterology</i> , 58, 1461-5, 2011	Population not with LARS. Includes patients who underwent sphincter-preserving surgery. Inclusion criteria not clear.
Martellucci, J., Low Anterior Resection Syndrome: A Treatment Algorithm, <i>Diseases of the Colon and Rectum</i> , 59, 79-82, 2016	A narrative article suggesting a treatment algorithm for LARS. No relevant data presented but references checked.
Mege, D., Meurette, G., Vitton, V., Leroi, A. M., Bridoux, V., Zerbib, P., Sielezneff, I., Sacral nerve stimulation can alleviate symptoms of bowel dysfunction after colorectal resections, <i>Colorectal Disease</i> , 19, 756-763, 2017	No comparison group. Only 31% of the participants had had rectal cancer.
Nct., Effect of Treatment of Low Anterior Resection Syndrome After Rectal Cancer Surgery, https://clinicaltrials.gov/show/nct03215017 , 2017	Clinical trial entry
Nct., Effectiveness of Sacral Neuromodulation in Low Anterior Resection Syndrome, https://clinicaltrials.gov/show/nct03598231 , 2018	Clinical trial entry
Ng, S. S. M., Leung, W. W., Mak, T. W. C., Futaba, K., Lee, J. F. Y., Electroacupuncture combined with fast-track perioperative program for reducing duration of postoperative ileus and hospital stay after laparoscopic colorectal surgery: A randomized controlled trial, <i>Colorectal Disease</i> , 20 (Supplement 4), 141, 2018	Conference abstract
Park, J. M., Angenete, E., Bock, D., Danielsen, A. K., Gehrman, J., Haglind, E., Rosenberg, J., Health economic analysis in a randomized trial of early closure of a temporary ileostomy after rectal resection for cancer (easy trial), <i>Diseases of the Colon and Rectum</i> , 61 (5), e197-e198, 2018	Conference abstract
Park, J., Danielsen, A. K., Angenete, E., Bock, D., Marinez, A. C., Haglind, E., Jansen, J. E., Skullman, S., Wedin, A., Rosenberg, J., Quality of life in a randomized trial of early closure of temporary ileostomy after rectal resection for cancer (EASY trial), <i>The British journal of surgery</i> , 105, 244-251, 2018	Population not relevant.
Pucciani, F., A review on functional results of sphincter-saving surgery for rectal cancer: the anterior resection syndrome, <i>Updates in surgery</i> , 65, 257-63, 2013	A narrative review of functional results and anterior resection syndrome after sphincter-saving

	surgery for rectal cancer. No relevant data.
Pucciani, F., Ringressi, M. N., Redditi, S., Masi, A., Giani, I., Rehabilitation of fecal incontinence after sphincter-saving surgery for rectal cancer: encouraging results, <i>Dis Colon Rectum</i> , 51, 1552-8, 2008	No relevant comparison group.
Ramage, L., Qiu, S., Kontovounisios, C., Tekkis, P., Rasheed, S., Tan, E., A systematic review of sacral nerve stimulation for low anterior resection syndrome, <i>Colorectal Disease</i> , 17, 762-71, 2015	A systematic review of sacral nerve stimulation for LARS. No comparative studies included.
Ridolfi, T. J., Berger, N., Ludwig, K. A., Low Anterior Resection Syndrome: Current Management and Future Directions, <i>Clinics in Colon & Rectal SurgeryClin</i> , 29, 239-45, 2016	A narrative review of LARS and its management. References checked for relevance.
Rosen, H., Robert-Yap, J., Tentschert, G., Lechner, M., Roche, B., Transanal irrigation improves quality of life in patients with low anterior resection syndrome, <i>Colorectal disease</i> , 13, e335-8, 2011	No comparison group.
Schwandner, O., Sacral neuromodulation for fecal incontinence and "low anterior resection syndrome" following neoadjuvant therapy for rectal cancer, <i>International Journal of Colorectal Disease</i> , 28, 665-669, 2013	No comparison group.
Stephens, Jh, Hewett, Pj, Clinical trial assessing VSL#3 for the treatment of anterior resection syndrome, <i>ANZ journal of surgery</i> , 82, 420-427, 2012	Probiotic therapy not an intervention of interest according to the review protocol.
Thomas, G. P., Bradshaw, E., Vaizey, C. J., A review of sacral nerve stimulation for faecal incontinence following rectal surgery and radiotherapy, <i>Colorectal Disease</i> , 17, 939-942, 2015	A systematic review of sacral nerve stimulation for faecal incontinence in people who had rectal surgery and radiotherapy. No comparative studies included.
Tomita, R., Sacral nerve function in patients with soiling more than 10 years after low anterior resection for lower rectal cancer, <i>Hepato-Gastroenterology</i> , 56, 120-3, 2009	No relevant interventions and outcomes.
Troncoso, P., Vigorita, V., Garrido, L., Facal, C., Moncada, E., Ruano, A., De San Ildefonso, A., Casal, J. E., Preliminary results in the use of posterior tibial nerve stimulation in the treatment of Low Anterior Resection Syndrome, <i>Colorectal Disease</i> , 2), 44, 2015	Conference abstract
Vigorita, V., Rausei, S., Troncoso Pereira, P., Trostchansky, I., Ruano Poblador, A., Moncada Iribarren, E., Facal Alvarez, C., de San Ildefonso Pereira, A., Casal Nunez, E., A pilot study assessing the efficacy of posterior tibial nerve stimulation in the treatment of low anterior resection syndrome, <i>Techniques in Coloproctology</i> , 21, 287-293, 2017	No comparison group.
Williams, J. R., Grieco, M. C., Sanchez, J. E., Marcet, J. E., Rasheid, S. H., Sacral nerve stimulator use in a patient with low anterior resection syndrome, <i>Surgical Endoscopy and Other Interventional Techniques</i> , 28, 321, 2014	Conference abstract
Ziv, Y., Zbar, A., Bar-Shavit, Y., Igov, I., Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations, <i>Techniques in Coloproctology</i> , 17, 151-62, 2013	A narrative review of LARS and reconstruction methods for bowel anastomosis. No relevant data presented.

1 Appendix L – Research recommendations

2 Research recommendations for review question: What is the optimal 3 management of low anterior resection syndrome?

4 Why this is important

5 Lower anterior resection is a common surgical treatment for rectal cancer however around
 6 40% of people who have a resection will develop LARS. LARS is a collection of symptoms
 7 that can develop after resection of part of the rectum or after the removal of the entire
 8 rectum. The symptoms experienced can include faecal and gas incontinence, urgent and
 9 frequent bowel movements, and bowel fragmentation. In turn, these symptoms can have a
 10 major impact on quality of life with effects on physical and psychological health, as well as
 11 social and sexual relations. Little is known about the effectiveness of different treatments as
 12 only small single-arm trials and small observational studies have been conducted. Sacral
 13 nerve stimulation and trans-anal irrigation have shown some promising results but a
 14 randomised controlled trial is needed to assess their effectiveness compared to symptomatic
 15 treatment.

16 **Research recommendation in question format:** What is the effectiveness and safety of
 17 sacral nerve stimulation and trans-anal irrigation compared to symptomatic treatment for
 18 people with major low anterior resection syndrome?

19

Research question	What is the effectiveness of sacral nerve stimulation and trans-anal irrigation for people with major low anterior resection syndrome?
Importance to 'patients' or the population	LARS can have significant long-term impact on quality of life across a range of domains including social and sexual relations as well as physical and psychological health. As improvements in colorectal cancer treatments lead to better survival it is essential that interventions to reduce the impact of LARS are also developed.
Relevance to NICE guidance	NICE guidance provides advice on effective, good value healthcare, which covers the period following successful treatment of disease.
Relevance to NHS	People with LARS will continue to need healthcare to treat their symptoms and improving their quality of life will contribute to wider NHS objectives in relation to treatments for people with colorectal cancer. This will be particularly valuable for a condition for which there is currently very little clarity on the most effective means of management
National priorities	The NHS is committed to improving the care, treatment and support for everyone diagnosed with cancer. Determining the optimal treatment and improving the quality of life of people with LARS will contribute towards this goal.
Current evidence base	Small single-arm trials and observational studies
Equalities	N/A

20 *N/A: not applicable*

21

Criterion	Explanation
Population	Adults who have undergone treatment for rectal cancer and are currently experiencing symptoms associated with a diagnosis of major LARS

Criterion	Explanation
	Sub-group analysis according to the extent and type of initial treatment
Intervention	<ul style="list-style-type: none">• Sacral nerve stimulation• Trans-anal irrigation
Comparator	Symptomatic treatment
Outcomes	<ul style="list-style-type: none">• Quality of life• LARS score• Treatment-related morbidity• Patient acceptability
Study design	Randomised controlled trial
Timeframe	Follow-up for two years from randomisation (by this time the long-term effectiveness of the intervention should be known)

1 LARS: *low anterior resection syndrome*