Supplementary Material 7

Evidence of effectiveness - Level 2 synthesis – Additional tables

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Systematic reviews judged to be at high/unclear risk of bias or to overlap with a more up-to-date or comprehensive systematic review (n=5)	
Chase 2011 [1]	Intervention addressed: non-pharmacological, non-surgical and non-behavioural treatments of functional chronic constipation in children ROB assessment: Low ROB Reason for exclusion: Superseded by Ng 2016 for electrical stimulation.
Iacona 2019 [2]	Intervention addressed: invasive and non-invasive types of neuromodulation, including transcutaneous nerve stimulation ROB assessment: High ROB Reason for exclusion: Not low ROB
Heymen 2003 [3]	Intervention addressed: biofeedback treatment for pelvic floor dyssnergia ROB assessment: High ROB Reason for exclusion: Not low ROB
Lu 2015 [4]	Intervention addressed: transcutaneous electrical stimulation therapy ROB assessment: High ROB Reason for exclusion: Not low ROB
Vande Velde 2018 [5]	Aim: to give an overview on bowel problems in cerebral palsy children and to suggest a stepwise treatment approach. ROB assessment: High ROB Reason for exclusion: not low ROB
Studies judged not to meet inclusion criteria (n=40)	
Bae 2019 [6]	Aim: Pelvic floor dysfunction (PFD) is one of important causes of chronic constipation in children. We analysed clinical characteristics, the results of diagnostic tests, and treatments of PFD in children. Not a study of an intervention.
Colares 2016 [7]	Aim: To evaluate the impact of implementation of the bowel management programme on the quality of life in children with fecal incontinence (FI), in a hospital in northeastern Brazil. Non RCT, with mixed population of children with organic and idiopathic constipation; results not presented separately.
Croffie 2005 [8]	Aim: to determine whether biofeedback benefits children with dyssynergic defecation and constipation/encopresis.

	Does not meet eligibility criteria.
Costigan 2014 [9]	Aim: To evaluate success of Peristeen transanal irrigation system. This survey study investigates the continued use of a transanal irrigation system, rather than effectiveness
Coulter 2002 [10]	Aim: A systematic review exploring the efficacy of biofeedback in the treatment of gastrointestinal problems. None of the included studies focussed on children with constipation.
Cucchiara 1984 [11]	Aim: To determine motility characteristics of the anorectum and to measure transit time. This study is not about effectiveness of treatment – not relevant
de Lorijn 2004 [12]	Aim: To investigate relationship between colonic transport time and symptoms. And outcomes at 1 year follow up; importance of symptoms in predicting outcome. This study is not about effectiveness of treatment – not relevant
Desantis 2011 [13]	Aim: A systematic review exploring the effectiveness of biofeedback for dysfunctional elimination syndrome (DES). Focussed specifically on DES, not functional constipation, therefore excluded.
Freedman 2014 [14]	Retrospective cohort, focussed on children who received an enema in the emergency department. Not clear how many children had a diagnosis of chronic constipation. No relevant outcomes reported.
Habib 2019 [15]	Aim: To report the side effects of milk of magnesia in one patient, aged 9. This is a single case report – exclude.
Heemskerk 2017 [16]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis (ongoing study).
Janssen 2016 [17]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Janssen 2018 [18]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Lee 2007 [19]	Aim: To determine the incidence and clinical aspects of allergic proctitis (AP) in infants with symptoms that mimic Hirschsprung's disease (HD). This study is not about treatment of chronic functional constipation – not relevant.
Librizzi 2017 [20]	Aim: to evaluate practice patterns and patient outcomes for the hospital management of functional constipation in US children's hospitals. This study is not about effectiveness of treatment – not relevant.
Lu 2016 [21]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Lu 2017 [22]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
NCT01823848 [23]	A trial of three types of enemas used to treat functional constipation in children Trial was terminated with no patients enrolled.
Mostamand 2019 [24]	Aim: To evaluate the effects of abdominal massage on colonic motility in patients receiving colonic manometry

	testing for various indications. Cohort study – focussed on participants with organic causes of constipation (only two participants with CFC).
Núñez Sánchez 2017 [25]	Aim: To report a case of severe toxicity of phosphate enemas in a child with no risk factors. This single case study is not about effectiveness of treatment – not relevant
Orhan 2018 [26]	Focus is on connective tissue manipulation and kinesio-taping. This study has been moved and included in the 'Complementary' therapy synthesis.
Panaite 2016 [27]	Not about effectiveness of treatment – not relevant
Peeters 2011 [28]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Penuelas Calvo 2016 [29]	Aim: To present a clinical case of an 11-year-old girl, with a diagnosis of functional encopresis with constipation and overflow incontinence for 4 years. This is a single case report – exclude.
Raghu 2019 [30]	Aim: to collect baseline data on the management of constipation at our hospital, use these data to develop and assess a clinical pathway for constipation management. Not relevant to this review – included in Service Provision review.
Rodriguez 2013 [31]	Aim: to evaluate the relationship between baseline colonic motility and response to the ACE, to evaluate changes in colonic motility after the ACE procedure, and to correlate colon motility parameters and their changes with the ability to decrease and eventually discontinue the ACE. this study is about evaluation of colon manometry changes and their utility on predicting ACE outcomes, rather than effectiveness of ACE. Not relevant.
Ruan 2018 [32]	Retrospective cohort, focussed on children who received an enema in the emergency department. Not clear how many children had a diagnosis of chronic constipation. No relevant outcomes reported.
Russell 2015 [33]	Focus is on provision of a management programme, so this study has been moved and included in the 'Care provision' synthesis.
Sanders 2014 [34]	Aim: To explore professionals' understanding and parents' experiences of using transanal irrigation with children at home as a mid to longer term bowel management approach. Qualitative study exploring experiences of transanal irrigation. Not focussed on effectiveness, therefore exclude.
Santucci 2020 [35]	Aim: To assess the relationship between self-efficacy, the belief that an individual can succeed at a goal, and short-term treatment outcome in children with functional constipation. This study is not about effectiveness of treatment – not relevant
Southwell 2020 [36]	Aim: A systematic review exploring evidence of electrical stimulation used to treat colonic disorders. This is a review of reviews, so does not meet our eligibility criteria.

Stephens 2018 [37]	Aim: To investigate constipation-related health care among children before and after constipation admission. This is about number of constipation-related outpatient visits and spending for those visits - not relevant. Included in review of economic evaluation.
Sulkowski 2015 [38]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Tambucci 2019 [39]	Aim: to evaluate the clinical impact of colonic transit scintigraphic studies in children with FC. This study is not about a treatment of CFC – it is about evaluating CTC impact - not relevant.
Heemskerk 2018 (NCT02961582) [40, 41]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis (ongoing study).
Unknown 2020 (NCT03819062) [42]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis (ongoing study).
Van der Wilt 2017 [43]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Van der Wilt 2014 [44]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Van der Wilt 2016 [45]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Van Wunnik 2012 [46]	Focus is on neuromodulation, so not relevant to Level 2. This study has been included in Level 3 synthesis.
Non-randomised studies focussed on an intervention which is covered by a systematic review (of electrical stimulation)(n=24)	
Clarke 2012 [47]	Aim: To determine whether transcutaneous electrical stimulation using interferential current (IFC) applied to the abdomen increased colonic propagating sequences in children with slow transit constipation. Cohort study focussed on electrical stimulation
Gunawan 2017 [48]	Aim: To determine proof of principle of whether a new home- based electrical stimulation device (Rhythm.IC) is safe and effective to reduce symptoms of chronic constipation in children after 4 months' stimulation. Non comparative study for electrical stimulation
Jordan-Ely 2013 [49]	Aim: to pilot a novel nurse-led method using combined highdose medication and TES Non comparative study for electrical stimulation
Leong 2011 [50]	Aim: To determine long-term outcomes for STC children treated by TES Cohort study for electrical stimulation
Lu 2016b [51]	Aim: to evaluate the efficacy of SNS in children with constipation treated with ACE Cohort study for electrical stimulation
Lu 2018 [52]	Aim: To evaluate the long-term efficacy of SNS in children with constipation Cohort study for electrical stimulation
Rego 2019 [53]	Aim: to assess the applicability and clinical outcomes of transcutaneous PTNS in children with functional intestinal constipation
Simmonds2015 [54]	Aim: We report a clinical audit to help inform practice development and future research.

	Non-comparative study for electrical stimulation
Southwell 2014 [55]	Aim: To determine if TES administered at home can improve STC in children Cohort study for electrical stimulation
Southwell 2012 [56]	Aim: to assess the effect of Transcutaneous electrical stimulation (TES) therapy on gastric emptying in slow-transit constipation children using nuclear transit scintigraphy. Cohort study for electrical stimulation
Veiga 2013 [57]	Aim: To evaluate the efficacy of parasacral transcutaneous electrical nerve stimulation for the treatment of constipation in children with lower urinary tract dysfunction. Cohort study for electrical stimulation
Yee 2011 [58]	Aim: to determine if TES use affected appendicostomy-formulation rates and to monitor changes in practice. Cohort study for electrical stimulation
Yik 2012a [59]	Aim: to test the effectiveness of home transcutaneous electrical stimulation (TES) when patients with slow-transit constipation (STC) were trained by a naive clinician. Cohort study for electrical stimulation
Yik 2012b [60]	Aim: to test the effectiveness of home transcutaneous electrical stimulation (TES) when patients with slow-transit constipation (STC) were trained by a naive clinician. Cohort study for electrical stimulation
Yik 2018 [61]	Aim: To examine the effectiveness of stimulation (TES) for six months Cohort study for electrical stimulation
Yik 2013a [62]	Aim: to test the effectiveness of TES to treat children with AR in a pilot study. Cohort study for electrical stimulation
Yik 2013b [63]	Aim: Determine the effects of daily TES-IFC delivered at home on bowel symptoms in children with slow transit constipation (STC). Controlled before and after study for electrical stimulation
Yik 2012c [64]	Aim: to assess gastrointestinal transit (GIT) in STC children after medical treatment and homebased TES, with nuclear transit scintigraphy (NTS) as an objective assessment. Controlled before and after study for electrical stimulation
Yik 2012d [65]	Aim: To compare MT and TES in two groups of children with STC using the Nuclear Transit Study (NTS) before and after treatment courses Controlled before and after study for electrical stimulation
Yik 2012e [66]	Aim: To assess symptoms and laxative use in STC children before and after home-based TES

	Controlled before and after study for electrical stimulation
Yik 2012f [67]	Aim: To investigate the effects of daily stimulation delivered at home on bowel symptoms in STC children Controlled before and after study for electrical stimulation
Yik 2012g [68]	Aim: to assess the end-users' responses and views to TES
Yik 2016 [69]	Aim: to test if TES can improve symptoms in children with chronic constipation without STC Pilot study for electrical stimulation
Zivkovic 2017 [70]	Aim: To evaluate the effects of interferential current (IC) stimulation and diaphragmatic breathing exercises (DBEs) in children with bladder and bowel dysfunction Non-RCT for electrical stimulation

Table 2: Characteristics of ongoing studies

Study	Aim	Study design	Anticipated completion date
Systematic reviews (n=3)			
Pacili 2017 [71]	To review results of using transanal colonic irrigation in providing effective bowel management	Systematic Review	30.03.18
Van Biervliet 2019 [72]	To assess the effectiveness of transanal irrigation using a rectal balloon	Systematic Review	31.10.2019
Van Engelenberg 2016 [73]	Physiotherapy interventions for functional bladder and bowel dysfunctions in neurologically normal and otherwise healthy children	Cochrane systematic review	Not stated
RCTs (n=5)			
Madhale 2018 [74] CTRI/2018/08/015415	To investigate the effect of matrix rhythm therapy in chronic functional constipation in children.	RCT	No date specified.
Feng 2014 [75] NCT02255747	To evaluate the effect of anal dilation in infants and children with constipation.	RCT	October 2016. No publications found.
EUCTR2010-023538-22-IS [76]	The primary objective of this trial is to investigate the laxative effect of Lysisstílar (Free Fatty Acids suppositories) as compared to Klyx	RCT	Reported as completed but no data. https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-023538-22
Ladi-Seyedian 2022 [77] [78] IRCT20140527017	Effects of transcutaneous functional electrical stimulation with or without biofeedback on functional non-	RCT	This was fully reported in March 2022. We have referred to this within the narrative synthesis.

876N4	retentive fecal incontinence in children		
Satish Joshi 2019 [79] CTRI/2019/06/019559	To explore effectiveness of conventional physical therapy along with structured physical therapy versus conventional physical therapy on constipation in children with neurodevelopmental disorder	RCT	Not stated (study registered on 10-06-2019). No publication found.

Table 3: Studies awaiting assessment for inclusion in Level 2 synthesis

Study (n=1)	Reason still awaiting assessment
Loening-Baucke 1995 [80]. Biofeedback treatment for chronic constipation and encopresis in childhood: long-term outcome. Pediatrics 1995; 96:(1 Pt 1)105-10.	Unable to access interlibrary loan

Table 4: Risk of bias of included systematic reviews, using the ROBIS tool

	Domain 1: concerns regarding specification of study eligibility criteria	**Domain 2: Concerns regarding methods used to identify and/or select studies**	**Domain 3: Concerns regarding methods used to collect data and appraise studies**	**Domain 4: Concerns regarding the synthesis and findings**	**Overall risk of bias in the review**
Ng 2016 [81]	LOW risk	LOW risk	LOW risk	LOW risk	LOW risk

Table 5: Risk of bias of RCTs included in updated systematic review

	Random sequence generation	**Allocation concealment**	**Blinding of particpants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**
Chase 2015 (assessed by Ng 2016 [81])	Unclear risk	Unclear risk	High risk	High risk	High risk	Low risk	High risk
Sharifi-Rad 2018 [82]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Table 6: Risk of bias judgements for included RCTs, using Cochrane ROB1 tool

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)
Awan 2021 [83]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk
Bekkali 2009 [84]	Low risk	Unclear risk	Unclear risk	High risk	Low risk
Borowiz 2002 [85]	Low risk	Unclear risk	High risk	High risk	Low risk
Bongers 2009 [86]	Low risk	Unclear Risk	Unclear risk	High Risk	Low Risk
Garcia 2016 [87]	Unclear risk	Unclear risk	Unclear risk	Low risk	High Risk
Loening-Baucke 1990 [88]	High risk	Unclear risk	Unclear risk	High risk	Unclear risk
Nolan 1998 [89]	Low Risk	Low risk	Unclear Risk	Low Risk	Low Risk
Ormarsson 2016 [90]	Low risk	Low risk	Low risk	Low risk	Unclear risk
Silva 2013 [91]	Low risk	Low risk	Unclear risk	High risk	Low risk
Strisciuglio 2021 [92]	Low risk	Low risk	High risk	High risk	Low risk
Van der Plas 1998 [93]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk
Van Engelenburg 2017 [94]	Low risk	Low risk	Unclear risk	Low risk	Low risk
Van Summeren 2020 [95]	Low risk	Low risk	High risk	High risk	Low risk
Wald 1987 [96]	Unclear Risk	Unclear Risk	High Risk	Low Risk	High Risk

Table 7: Risk of bias judgements for cohort studies, using CASP tool for cohort Studies

Study	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have they taken account of the confounding factors in the design and/or analysis?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	Do you believe the results?	Can the results be applied to the population of interest?	OVERALL ASSESSMENT
Awan 2016 [97]	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell	Yes	Yes	Yes	Yes	Minor concerns
Jarzebicka 2016 [98]	Yes	Yes	No	Can't tell	Yes	No	Can't tell	yes	No	No	Serious concerns
Jorgensen 2017 [99]	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Can't tell	Moderate concerns
Loening-Baucke 1993 [100]	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Serious concerns
Modin 2016 [101]	Yes	Can't tell	Can't tell	Yes	Can't tell	No	Can't tell	Can't tell	Yes	Can't tell	Serious concerns
Nader 2016 [102]	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Serious concerns
Nasher 2014 [103]	Yes	Yes	Can't tell	Yes	No	No	No	Yes	Can't tell	Can't tell	Serious concerns
Patel 2019 [104]	Can't tell	Yes	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	No	Serious Concerns
Raffaele 2015 [105]	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Serious concerns
Sharma 2016 [106]	Yes	Yes	Can't tell	Can't tell	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Can't tell	Serious Concerns

Wainganka r 2018 [107]	Yes	Can't tell	Can't tell	Can't tell	No	No	Can't tell	Can't tell	Can't tell	Yes	Serious concerns
Yoo 2017 [108]	Yes	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Can't tell	Can't tell	Moderate concerns

Table 8: Risk of bias judgements of cross sectional studies, using JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies tool

Study	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
Koppen 2017 [109]	Yes	Yes	Unclear	Yes	No	No	No	Yes
Eisenberg 2009 [110]	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Table 9: Risk of bias judgements of studies with other designs, using WEIRD tool

Study	Is there a clearly stated aim, objective or purpose for the source material?	Is there a clear description of the source of the information reported (transparency)?	Is there a clear description of the programme or intervention or policy or reform on which the source material focuses?	Is there a clear description of the context/s to which the information described in the source material relates?	Is the information accurate (source materials other than empirical studies)?	Is the information accurate (empirical studies only)?	Is the evidence representative?	Are any limitations of the information and / or methods discussed in the source material?	Is evidence provided to support any findings or conclusions made?	Are relevant rights and ethics considerations described?	Are any interests declared and any potential conflicts of interest noted?	Overall Assessment
Loening-Bauke (i) 1989 [111]	Yes	No	Unclear	Unclear	NA	Yes	Unclear	Unclear	yes	Yes	yes	Moderate concerns

Table 10: Outcomes - comparisons of outcomes from Ng 2016 [81] and Sharifi-Rad 2018 [82]

Outcomes relevant to our review	**Outcomes analysed in Ng 2016 [81] (based on inclusion of Chase 2015)**	**Outcome data reported in Sharif Rad 2018 [82] (reported as median, IQR)***
Painful defecation		Pain score (0-10)
QoL of parents & patients	Improved QoL Self-perceived QoL* Parent perceived QoL	QoL scores*
Defecation frequency		Defecation frequency per week
Stool consistency		
Side effects		
Faecal incontinence	Improved symptoms relating to soiling*	Faecal soiling episodes per day*
Abdominal pain		
School attendance		
	Improve spontaneous bowel movement	
	Improved colonic transit	
	Colonic transit rate	
		Constipation score (0-29)

*Outcome combined within meta-analyses

Table 11: Reported Outcomes of Included RCTs and primary studies

	Outcomes Addressed								
Study	**Painful Defecation**	**QOL**	**Stool Frequency**	**Stool Consistency**	**Side Effects**	**Faecal Incontinence**	**Abdominal Pain**	**School Attendance**	**Other**
Awan 2016 [97]			x						Constipation severity scale, spasticity
Awan 2021 [83]			x						Constipation severity scale, spasticity
Bekkali 2009 [84]			x	x		x	x		Behaviour score. Colonic transit time. "Successful disimpaction"
Bongers 2009 [86]	x	x	x			x	x		Overall treatment success, laxative use
Borowitz 2002 [85]			x			x			Amount of laxative; cured or improved (soiling)
Eisenberg 2009 [110]			x						Defined constipation as “2 bowel movements per week, or 2 of the following on more than one occasion: straining, hard stools, feeling of incomplete evacuation”
Garcia 2016 [87]					x		x		Disimpaction
Jarzebicka 2016 [98]			x	x		x			Clinical improvement. Amplitudes between the extreme and the basic pressure.
Jorgensen 2017 [99]						x			
Koppen 2017 [109]					x	x			Parent satisfaction
Loening-Baucke 1990 [88]			x			x			Anorectal manometry; studies of balloon defecation; studies of the effects of rectal distension
Loening-			x	x			x		Treatments

Baucke 1993 [100]									
Loening-Bauke (i) 1989 [111]						x			Recovery defined as to be off laxatives for one month, have ≤2 soils per month and ≥3 bowel movements per week.
Modin 2016 [101]			x	x		x	x		Behavioural difficulties, treatment success
Nader 2016 [102]						x			Need and Envy score
Nasher 2014 [103]		x			x	x			
Nolan 1998 [89]					x	x			Laxative remission, Rectal hyposensitivity, Behaviour problem scores. Number of improved participants.
Ormarsson 2016 [90]			x				x		Time until bowel movement, amount of faeces, amount of blood, amount of mucus discharge
Patel 2019 [104]						x	x		Continued cecostomy use. Constipation (not defined)
Raffaele 2015 [105]							x		Constipation score
Sharma 2016[106]		x			x	x		x	Improvement in chronic constipation.
Silva 2013 [91]	x		x	x	x	x			Straining during defecation. Withholding behaviour.
Strisciuglio 2021 [92]		x	x	x					Dose of product, gastrointestinal symptoms
Van der Plas 1998 [93]			x			x			Anorectal manometry; overall treatment success
Van Engelenburg 2017 [94]		x							Absence of FC according to Rome III criteria; Global perceived effect (rating scale); use of laxatives
Van Summeren 2020 [95]		x							Laxative use, general health status, global perceived treatment effect, costs.
Waingankar	x			x			x		Maintenance of the diet, severity of constipation

2018 [107]									
Wald 1987 [96]			x			x			Clinical outcome (including defecation frequency, FI frequency, soiling frequency, parental perception of clinical status and overall satisfaction). Sensorimotor function. Outcomes categorised into no improvement, some improvement, marked improvement and complete remission.
Yoo 2017 [108]			x		x		x		

Table 12: Studies addressing questions relating to Level 2 of the pyramid

Main heading	**Pharmacological**			**Other**					**Lifestyle**	**Combined**
Sub-heading	Enemas			Neuromodulation	Irrigation	Biofeedback	Physiotherapy		Diet	Pharmacological + Lifestyle + Information + Psychosocial
Question addressed	*What is the effect of rectal enemas in children with severe constipation?*	What is the difference in effectiveness of microenemas and oral laxatives for functional constipation in infants?	What is the difference in effectiveness of an enema and a soft suppository for disimpaction?	*What is the effectiveness of transcutaneous electrical stimulation?*	*What is the effect of transanal irrigation?*	What is the effect of biofeedback?	*What is the effect of physiotherapy, in combination with conventional treatment?*	*What is the effectiveness of physical rehabilitation for children with cerebral palsy?*	*What is the effect of dietary exclusion of fructose and lactose?*	*What is effect of a combined therapeutic programme?*
Systematic reviews (n=1)				***Ng 2016*** [81]						
RCTs to be added to systematic review (n=1)				Sharifi Rad 2018 [82]						
RCTs (n=14)	Bongers 2009 [86]	Strisciuglio 2021 [92]	Ormarsson 2016 [90]			Nolan 1998 [89]	Silva 2013 [91]	Awan 2021 [83]		Borowitz 2002 [85]

	Bekkali 2009 [84] Garcia 2016 [87]					Loening-Baucke 1990 [88] Van der Plas 1998 [93] Wald 1987 [96]	Van Engelenburg 2017 [94] Van Summeren 2020 [95]			
Other primary studies (n=15)	Yoo 2017 [108]				Nasher 2014 [103] Koppen 2017 [109] Sharma 2016 [106] Patel 2019 [104] Jorgensen 2017 [99]	Jarzebicka 2016 [98] Raffaele 2015 [105] Nader 2016 [102]		Awan 2016 [97] Eisenberg 2009 [110]	Waingankar 2018 [107]	Loening-Baucke 1989 [111] Loening-Baucke 1993 [100] Modin 2016 [101]

Table 13: Judgement of certainty in evidence and summary of findings relating to each research question

Question	Study	Limitations	Inconsistency	Indirectness	Imprecision	Publication	Judgement	Summary of

	designs					**bias**	**certainty in evidence**	**findings**
What is the effect of rectal enemas in children with severe constipation?	RCTs; Bongers 2009 [86]; Bekkali 2009 [84]; Garcia 2016 [87] Cohort study: Yoo 2017 [108]	Downgrade once due to unclear / high ROB on some domains;	Downgrade once differences in populations and interventions	No downgrade	Downgrade once – lack of results data presented.	No downgrade	VERY LOW	There is very low certainty that the addition of regular rectal enemas may increase defecation frequency, but not have any effect on overall treatment success or other outcomes, and may cause discomfort or distress to some. There is insufficient evidence to reach any conclusions about the relative effect of different types of enemas or the effectiveness of specific regimens.
What is the difference in effectiveness of microenemas and	RCT: Strisciuglio 2021 [92]	Downgrade once due to unclear / high ROB on some	No downgrade – consistent findings	No downgrade	No downgrade	No downgrade	LOW	There is low certainty from one RCT that Promelaxin

oral laxatives for functional constipation in infants?		domains; Downgrade once as only 1 RCT						microenemas and oral laxatives are equally effective in the treatment of functional constipation in infants (6-48 months).
What is the difference in effectiveness of an enema and a soft suppository for disimpaction?	RCT: Ormarsson 2016 [90]	Downgrade once –low participant numbers	No downgrade – consistent findings (only one study)	Downgrade once – limited outcomes assessed	No downgrade	No downgrade	LOW	There is low certainty from one RCT that enemas and high dose suppositories were equally effective at promoting bowel emptying.
What is the effect of transcutaneous electrical stimulation?	Updating of Ng 2016 [81], which contained one RCT (Chase 2015). Addition of one RCT (Sharifi-Rad 2018 [82])	Downgrade once due to unclear / high ROB on some domains. For QoL: Downgrade once due to need to estimate mean and SD from median and IQR.	Downgrade once – different methods of measuring soiling / QoL	No downgrade	For soiling episodes: downgrade once – low number of events.	No downgrade	VERY LOW	There is very low certainty that TES may reduce the number of soiling episodes and improve self-reported quality of life, as compared to sham TES.
What is the Effect of Transanal Irrigation?	Primary Studies:	Downgrade once as all studies	No downgrade – consistent findings	One downgrade – studies	Downgrade once – lack of statistical	No downgrade	VERY LOW	There is very limited evidence about the

	Nasher 2014 [103] Patel 2019 [104] Koppen 2017 [109] Sharma 2016 [106] Jorgensen 2017 [99]	high/moderate ROB; downgrade once due to number of participants		measured different outcome measures, and had different populations, and different co-treatments	data presented			effectiveness of transanal irrigation. There is some very low certainty evidence that transanal irrigation may be safe, feasible and effective for children with intractable symptoms which have not resolved with long term conventional laxatives and management.
What is the effect of biofeedback?	<u>RCTs:</u> Nolan 1998 [89]; Loening-Baucke 1990 [88]; Wald 1987 [96]; Van der Plas 1998 [93] <u>Cohort study:</u> Jarzebicka 2016 [98]; Nader 2016 [102]; Raffaele 2015 [105]	Downgrade once due to unclear / high ROB for some domains;	Downgrade once – some inconsistency in findings	Downgrade once – RCTs had different comparison groups. In one study this was an alternative / active treatment	No downgrade	No downgrade	VERY LOW	There is some limited evidence about the effectiveness of biofeedback, suggesting that there may be no additional benefit of supplementing conventional treatment with biofeedback therapy in children with normal

								defecation dynamics, but potentially some benefit for the subgroup of children with abnormal defecation dynamics. We have very low confidence in this finding.
What is the effect of physiotherapy, in combination with conventional treatment?	RCTs: Silva 2013 [91]; van Engelenburg 2017 [94]; van Summeren 2020 [95]	Downgrade once due to unclear / high ROB for some domains	Down grade once – inconsistent findings between studies	One downgrade – studies measured different outcome measures	No downgrade	No downgrade	VERY LOW	Evidence relating to the effectiveness of physiotherapy is inconsistent. Evidence does not support the routine referral to physiotherapy for all children with constipation seen within primary care. There is some limited evidence that physiotherapy may be beneficial for a subgroup of children, but

								further research is required to confirm (or refute) this. We have very low confidence in this finding.
What is the effectiveness of physical therapy for children with cerebral palsy?	RCT: Awan 2021 [83] cohort: Awan 2016 [97], Eisenberg 2009 [110]	Downgrade twice due to high ROB of studies, and low participant numbers	Downgrade once – different interventions studied	No downgrade	No downgrade	No downgrade	VERY LOW	There is some very low quality evidence to suggest that constipation in children with cerebral palsy may be improved with physical therapy. However, evidence is insufficient to support generalised conclusions.
What is the effect of dietary exclusion of fructose and lactose?	Primary study - Waingankar 2018 [107]	Downgrade once due to low participant numbers. Downgrade once due to risk of bias of study design	No downgrade – consistent findings (only one study)	No downgrade – single study	Downgrade once – data from one study collected from retrospective case notes	No downgrade	VERY LOW	There is limited, very low certainty evidence that exclusion of fructose and lactose, with expert health professional

								advice, could reduce severity of constipation. However, implementation of this diet was challenging. Further research is required.
What is the effect of a combined treatment programme?	Borowitz 2002 [85] Loening-Baucke 1989 [111] Loening-Baucke 1993 [100] Modin 2016 [101]	Downgrade once due to risks of bias; Downgrade once due to low participant numbers	Downgrade once – consistency difficult to judge due to differences between studies	Downgrade once due to lack of intervention details, and differences between studies	No downgrade	No downgrade	VERY LOW	There is insufficient evidence to support specific conclusions relating to the effect of a combined treatment programme but some very low certainty evidence that these may be beneficial for some children.

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