Appendix 1. Studiekarakteristieken initiële medicamenteuze behandeling

Study ID	**Participants** (age, number, definition FC)	**Interventions** (dosage, treatment period, concomitant therapy)	**Treatment success** (definition + time of measurement)	**Withdrawals due to AE**	**Defecation frequency** (definition + time of measurement)
Rectal enema vs PEG (oral)					
Bekkali 2009	Age 4 – 16 years, N=90 FC definition: Rome III FI definition: large amount of hard stool in the rectum (fecaloma)	Rectal enema: dioctylsulfosuccinate sodium, once daily for 6 days (60 ml children < 6 years, and 120 ml for children of 6 years and older) PEG (oral): PEG3350 + electrolytes 1.5 gr/kg per day for 6 days. Maintenance therapy was started in both groups after 6 days of disimpaction: PEG3350 + electrolytes 0.5 g/kg/day for at least 2 weeks (follow-up period)	Def: absence of fecaloma on digital rectal examination (DRE). If children scared to undergo second DRE, X-ray performed Time: 6 days	Reported Time: 3 weeks	Def: frequency per week, mean (SD) Time: 3 weeks (2 weeks after week of disimpaction treatment)

AE: adverse events, FC: functional constipation, FI: fecal impaction, DRE: digital rectal examination

Appendix 2. Studiekarakteristieken onderhoudstherapie medicamenteuze behandeling

Study	**Participants** (age, number, definition FC)	**Intervention** (dosage, treatment duration, concomitant therapy)	**Treatment success** (definition + time of measurement)	**Withdrawals due to AE**	**Defecation frequency** (definition + time of measurement)
PEG vs Lactulose					
Dheivamani 2021	Age 2 – 12 years, N=100, Rome IV	PEG vs lactulose Dosage: PEG 3350 0.7 g/kg once/day Lactulose 0.7 g/kg once/day Treatment duration: 4 weeks	Def: Response rate: more than 2 bowel movements per week Time: 4 weeks	Reported	Def: frequency per week, mean (SD). Time: 4 weeks
Dupont 2005	Age 6 months – 3 years, N=98, FC defined as '< 1 stool per day for more than 1 month in children 6 - 12 months old and < 3 stools per week for more than 3 months in children aged 13 months - 3 years'	PEG 4000: one sachet of 4 g/sachet Lactulose: one sachet of 3.33 g/sachet. Dose could be increased. Treatment duration: 3 months	NR	Reported	Def: frequency per week, median (IQR). Reported separately for ages 6 months – 12 months and 13 months – 3 years Time: 3 months
Jarzebicka 2019	Age 6 months – 6 years, N=102, Rome III	PEG: up to 8 kg, 5 g/day; 8 to 12 kg, 10 g/day; 12 to 20 kg, 15 g/day; >20 kg, 20 g/day, divided as 2 doses. Lactulose: 1 mL/kg, twice a day. 4 weeks	Def: 3 or more stools per week and an improvement in stool consistency of at least 2 types in the Bristol scale were considered good clinical outcome Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: at week 4
Saneian 2012	Age 1 – 16 years, N=90, Rome III	PEG: 1 cc /kg/day Lactulose: 1 cc /kg/day MgOH: 1 cc /kg/day Dosage could be increased to 3 cc/kg/day)	Def: defecation equal or more than 3 times a week without pain and bleeding, in addition with fecal incontinence less than twice a month at the end of one month treatment. No data reported	NR	Def: increase in frequency per week (SD) Time: 4 weeks

		Treatment duration: 4 weeks Patients were disimpacted at start of treatment if necessary.			
Treepongkaruna 2014	Age 12 months – 36 months, N=88, FC defined as 'either a stool frequency of ≤2 per week persisting for at least 3 months OR the presence of pebble-like, hard stools, painful defecation or faecal incontinence for at least 3 months'	PEG 4000: 8 g per day Lactulose: 3,3 g per day 4 weeks	Not reported	Reported	Def: frequency per day, mean (SD) Time: 4 weeks
Uhm 2007 (translated from Chinese)	Age unclear. Only reported mean age at diagnosis: 5,5 years. N=56, FC defined according to IOWA-criteria	PEG 4000: 0,5 g/kg per day Lactulose: 1,5ml/kg daily, divided in two doses per day. Treatment duration: unclear. Patients could be weaned off medication during the 12 month study period.	Def: number of painless bowel movements without medication for at least one month. Number of painless bowel movements is at least 3 times per week, fecal incontinence is less than 2 times per month, and no abdominal pain. Time: after 12 months	Reported	NR
Voskuijl 2004	Age 6 months – 15 years, N=100, FC defined as 'at least 2 out of 4 of the following symptoms for the last 3 months: < 3 bowel movements per week; encopresis > 1/week; large amounts of stool every 7–30 days (large enough to clog the toilet); and palpable abdominal or rectal mass on physical examination.	PEG 3350: Between 6 months and 6 years of age: 2,95 g per day >6 years: 5.6 g per day Lactulose: Between 6 months and 6 years of age: 6 g >6 years: 12 g per day Treatment duration: 8 weeks	Def: defecation frequency >3/week and encopresis (1 or less every two weeks). Time: 8 weeks	Reported	Def: frequency per week, mean (SD) Time: 8 weeks

Wang 2007 (translated from Chinese)	Age 8 – 18 years, N=227, FC defined as 'passing type 1-3 stool as per Bristol stool chart and having ≤ 2 bowel motions for 2 consecutive weeks.	PEG 4000: 2 packs (20g) taken once a day Lactulose: 15ml once a day for three days, followed by maintenance dose of 10ml twice a day Treatment duration: 2 weeks	Def: Stool properties returned to normal Time: 2 weeks	NR	NR
PEG vs placebo					
Nurko 2008	Age 4 – 16 years old, N=103, FC defined as 'at least 3 months ≤ 3 spontaneous bowel movements (BM) per week and 1 or more associated symptoms that included straining, hard stools sensation of incomplete evacuation, production of large bowel movements that may obstruct the toilet, or painful defecation'	PEG 3350: 0.2 g/kg or 0.4 g/kg or 0.8 g/kg per day Placebo Treatment duration: 2 weeks	Def: three or more bowel movements during the second week of treatment Time: 2 weeks	Reported	Reported, but no exact data available for analysis.
Modin 2018	Age 2 – 16, N= 115, Rome III	PEG 3350: 0.8 g/kg per day Placebo: identical to PEG At least 8 weeks, after that patients could be weaned off medication	Def: the absence of any Rome III criteria, with or without use of medication Time: 24 weeks	Reported	Def: frequency per week, mean (SD) Time: 24 weeks
Thomson 2007	Age 2 – 11 years, N=51, Rome criteria	PEG 3350 + electrolytes: 6.9 g powder per sachet. Number of sachets depended on age and increased by a dosing regimen during the first week to 4 – 6 sachets per day. Placebo: identical to PEG	NR	NR	Def: frequency per week, mean (SD) Time: 2 weeks

		Dosage could be adjusted in the second week to determine a dose at which symptoms of constipation as defined by the Rome criteria noted above did not occur. Treatment duration: 2 weeks Children were excluded from the study if they had current or previous fecal impaction.			
PEG vs Magnesium hydroxide (MgOH)					
Gomes 2011	Age 1 – 15 years, N=38, Rome III	PEG 4000: 0.5 g/kg per day MgOH: 3 mL/kg per day Treatment duration: 6 months	NR	Reported	Def: frequency per week, mean (SD) Time: 6 months
Loening-baucke 2006	Age 4 – 18 years, N=79, Rome III	PEG 3350: 0.7 g/kg per day MgOH: 2 mL/kg Treatment duration: unclear, patients could be off medication at end of study	NR	Reported	Def: frequency per week, mean (SD) Time: 6 months
Ratanamongkol 2009	Age 1 – 4 years N=94,	PEG 4000: 0.5 g/kg MgOH: 3 mL/kg per day Treatment duration: unclear, patients could be off medication at end of study	Def: the proportion of patients who had ≥ three bowel movements per week, ≤ two episodes of fecal incontinence per month, and no painful defecation, with or without laxative therapy Time: 4 weeks	Reported	Def: frequency per week, median (IQR) Time: 4 weeks
PEG vs Liquid paraffin					
Karami 2009	Age 1 – 10 years, N=126, FC defined as 'stool	PEG: 0.8 g/kg twice per day Liquid paraffin: 1 cc/kg twice per day	NR	NR	Def: frequency per week, mean (SD) Time: 4 weeks

	frequency less than 2 times per week with fecal hard consistency, encopresis two or more than two times per month, palpable fecal impaction in abdomen or rectum'	Treatment duration: unclear			
Rafati 2011	Age 2 to 12 years, N=160, FC defined as 'less than 3 stools per week, more than 1 encopresis per week or palpable abdominal or rectal fecal mass on physical examination'	PEG 3350 1.0-1.5 g/kg per day Liquid paraffin: 1.0-1.5 ml/kg per day Treatment duration: 4 months	Unclear definition	Reported	Def: frequency per week, mean (SD) Time: 4 months
PEG vs Herbal medicine					
Dehghani 2019	Age 4 – 12 years, N=92, Rome III	PEG: syrup (40% w/v) with a dose of 1 mL/kg body weight/day Black Strap Molasses: syrup (40%w/v) with a dose of 1 mL/kg body weight/day Treatment duration: 4 weeks Concomitant therapy: toilet training and nutritional advice in both groups.	Def: not fulfilling the Rome III criteria Time: 4 weeks	Reported	Def: number of patients with ≤2 bowel movements/week Time: 4 weeks
Esmaeilidooki 2016	Age 2 – 15 years, N=109, Rome III	PEG 4000: 0.7 – 0.8 g/kg per day Cassia Fistula's Emulsion: 1 cc/kg per day Treatment duration: 4 weeks	Def: No longer fulfilling Rome III criteria Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

Nasri 2022	Age 2 – 15 years, N=120 Rome IV	PEG 4000: 0.7 g/kg (unclear if its 0.7 g/kg three times per day, or if 0.7 g/kg is divided in three times during the day) LaxaPlus Barij®: 1 mL/kg daily divided into three doses for <30 kg, 10 mL three times daily for >30 kg Treatment duration: 8 weeks	NR	Reported	Def: frequency, unclear if per day or per week, mean (SD) Time: 8 weeks
Imanieh 2022	Age 1 – 18 years, N=100, Rome IV	PEG: initial dosage was 1 ml/kg per day. R. damascene and brown sugar syrup: 0.1g damask rose petals and 0.85g brown sugar per 1 mL solution. Initial dosage was 1 ml/kg per day. Both groups: If no response, the dosage was increased to 2 ml/kg. Treatment duration: 4 weeks	Def: having fewer than two of the Rome IV criteria after treatment Time: 4 weeks	Reported	Def: number of patients with 2 or fewer defecations per week Time: 4 weeks
Nimrouzi 2015	Age 2 – 12, N=120, Rome III	PEG 4000: 0.4 g/kg per day D. Sophia seed: 2 g for 2-4 years old, 3 g for 4-12 years old Treatment duration: 8 weeks	Def: Improvement of constipation for at least 3 bowel movements, soft stool and convenient defecation, no soiling and bloody stool per week as well as exiting the Rome III criteria for constipation after the third week. Time: 8 weeks	Reported	Def: frequency per week, median (IQR) Time: 3 weeks
Saneian 2021	Age 2 – 15 years, N=60, Rome IV	PEG 4000: 0.7 g/kg per day Golghand®: 0.5 g/kg per day Treatment duration: 8 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 8 weeks

Tavassoli 2021	Age 4 – 10 years, N=140, Rome III	PEG: 1 g/kg per day Viola Flower Syrup: 5 cc 3 times per day Treatment duration: 4 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
PEG vs sodium picosulfate vs fibers					
Cassettari 2019	Age 5 – 10, N=80, Rome IV	Group 1: PEG 3350 + electrolytes, dosage NR Group 2: Sodium picosulfate, dosage NR Group 3: Green banana biomass (GBB), 30 g per day Group 4: PEG + GBB, dosage NR Group 5: Sodium picosulfate + GBB, dosage NR Treatment duration: 8 weeks Concomitant therapy: dietary advice	NR	NR	Reported as dichotomous outcome. Def: number of patients having more than 3 bowel motions as week. Time: after 8 weeks
Quitadamo 2012	Age 4 – 10 years, N=100, Rome III	PEG 3350 + electrolytes: 0,5 g/kg per day, increase up to 1.0 g/kg per day if necessary Fiber mixture: 16,8 g per day, increase up to 22,4 g per day if necessary Treatment duration: 8 weeks Concomitant therapy: disimpaction before start treatment. Rescue therapy: enemas if no defecation for > 3 days	Def: 3 or more bowel movements per week, 2 or higher stool consistency grade on BSFS, absence of fecal incontinence, abdominal pain, pain on defecation, and fecal bleeding. Time: 8 weeks	Reported	Def: frequency per week, mean (SD) Time: 8 weeks
PEG vs microenema					

Strisciuglio 2021 *Promelaxin microenema*	Age 6 months – 4 years, N=158, Rome III	PEG: 4 g/day 6-12 months and 4-8 g/day for 12-48 months age Promelaxin: 2.5 mg (2ml) for children 6-12 months, 5mg (4ml) for 12-48 months with a maximum of 10 g (8ml) was given daily Treatment duration: for 2 weeks. After these two weeks participants received the same daily dosage on-demand for 6 more weeks. On demand treatment was defined as the need for PEG or Promelaxin after 48 h without a fecal evacuation. Concomitant therapy: dietary and toilet training recommendation.	Def: at least 3 evacuations per week and an average increase of at least one evacuation per week as compared to baseline after two weeks of treatment. Time: 2 weeks	Reported	No data reported.
PEG vs prebiotics (with addition of probiotics)					
Foroughi 2022	Age 2 – 12 years, N=144, Rome IV	PEG: 6 g per day PEG + probiotics: 6 g per day + 109 CFU bac- terial probiotics (mixture of different stems) Prebiotics: Psyllium Seed Husk Powder 6 g per day Prebioitcs + probiotics: Psyllium Seed Husk Powder 6 g per day day + 109 CFU bac- terial probiotics (mixture of different stems) Treatment duration: 3 weeks Concomitant therapy: dietary advice and toilet training were provided to all parents.	NR	NR	Def: frequency per week, mean (SD) Time: 3 weeks

PEG4000 vs PEG3350 + electrolytes					
Bekkali 2018	Age 6 months - 16 years, N=97, FC defined as 'defecation frequency <3 times per week'	PEG4000: sachets containg 4g of PEG with a molecular weight of 4000g/mol PEG3350+Electrolytes: sachets containing 2.95 g of PEG with a molecular weight of 3350 g/mol and electrolytes: 37.5 mg potassium chloride, 73 mg sodium chloride, 284 mg sodium sulfate, and 84 mg sodium hydrogen carbonate. Treatment duration: 52 weeks Concomitant therapy: rectal enemas first 3 days of treatment. Rescue medication (enema or oral dose of 5mg bisacodyl) if defecation did not occur within 3 consecutive days.	Def: defecation frequency of ≥3 per week with <1 episode of fecal incontinence. Time: 52 weeks	Reported	Def: frequency per week, mean (SD) Time: 52 weeks
Savino 2012	Age 2 – 16 years, N=96, Rome III	PEG4000: 0.7 g/kg/day; in children >20 kg same daily dose with a maximum limit of 30 g daily. PEG3350+Electrolytes: 6.9 g per sachet. 1 sachet per day in children aged 2–6 years; 2 sachets in children aged 7–11 years; 4 sachets in children aged 12–16 years. Treatment duration: 4 weeks Concomitant therapy: disimpaction treatment was initiated if fecal impaction was established.	Def: resolution of faecal impactment and Adequate relief of constipation in terms of normalized frequency (≥3 BM per week). Time: 4 weeks No data reported, only in figure.	Reported	Def: frequency per week, mean (SD) Time: over the 4 weeks of treatment

Lactulose vs placebo					
Cao 2018	Age 2 – 6 years, N=100, Rome III	Lactulose: 5 ml (3,3 g) per day Placebo: same size, dose, color, flavor, and appearance Treatment duration: 6 weeks	NR	NR	Def: frequency per day change from baseline, mean. Unclear if spread is reported as range or SD. Time: 6 weeks
Lactulose vs lactitol					
Pitzalis 1995	Age 8 months – 16 years, N=51, chronic FC defined as 'less than 3,5 weekly evacuations'	Lactulose: 500 mg/kg/day as a single morning dose increased if necessary up to 750 mg/kg/day. Lactitol: 50 mg/kg/day as a single dose in the morning, increased if necesary to 400 mg/kg/day. Treatment duration: 4 weeks Dietary advice and education for toilet training were given to parents.	NR	NR	Def: frequency per week, mean (SD) Time: 4 weeks
Lactulose vs liquid paraffin					
Farahmand 2007	Age 2 – 12 years, N=247, FC defined as 'having at least two out of four of the following symptoms, for the last 3 months: < 3 bowel movements/week; fecal soiling > 1 times per week, large amounts of stool every 7-30 days and palpable abdominal or	Lactulose: 1-2 ml/kg twice per day Liquid paraffin: 1-2 ml/kg twice per day Treatment duration: 8 weeks At the first visit, patients received one or two enema daily for two days to clear any rectal fecal impaction. (30 cc / 10 kg weight of paraffin oil for enema.	Def: defecation frequency 3 or more per week and encopresis 1 or less every two weeks. Time: 8 weeks	Reported	Def: frequency per week, mean (SD) Time: 8 weeks

	rectal fecal mass on physical examination'	Dose adjustment: increase or decrease of volume of each drug by 25% every 3 days as required, to yield, 1 or 2, firm–loose, stools. Instructions were given to increase daily fiber intake to an amount of grams equal to their age plus 10.			
Urganci 2005	Age 2 – 12 years, N=40, chronic constipation defined as symptoms of at least 3 months duration including at least two of the following: hard stools, painful defecation, rectal bleeding, encopresis and fewer than three bowel movements per week.	Lactulose: 1 mL/kg, twice per day. Liquid paraffin: 1 mL/kg, twice per day. Treatment duration: 8 weeks Each drug was increased or decreased by 25% every 3 days as required, to yield, 1 or 2, firm– loose, stools. Instructions were given to increase daily fiber intake to an amount of grams equal to their age plus 10.	Def: clearance of the impaction (more than three bowel movements per week and improvement in stool consistency). Time: last 4 weeks of treatment	Reported	Def: frequency per week, mean (SD) Time: last 4 weeks of treatment
Lactulose vs fibers					
Kokke 2008	Age 1 – 13 years, N=135 , FC defined as 2 of 4 criteria: stool frequency less than 3 times per week, fecal incontinence 2 or more times per week, periodic passage of large amounts of stool at least once every 7 to 30 days, or a palpable abdominal or rectal mass	Lactulose: 10 g/125 mL Fiber mixture: 10 g/125 mL Patients with a weight <15 kg received 1 bottle (125 mL, 10 g fibers) daily, those with a weight between 15 kg and 20 kg received 2 bottles (250 mL, 20 g) daily, and those with a weight above 20 kg received 3 bottles (375 mL, 30 g) daily. The study product was taken at breakfast and, in the case of 2 or more bottles, also at lunch.	NR	Reported	Def: frequency per week. Unclear if median/mean. No measure of spread reported.

		Treatment duration: 8 weeks + 4 weeks weaning period. Total of 12 weeks. Enema was given in case of rectal impaction before start treatment. Rescue medication: macrogol 3350 in no improvement after 3 weeks. If persistent diarrhea was reported, the original dose was reduced by 50%.			
Üstündağ 2010	Age 4 – 16 years, N=68, Rome III	Lactulose: 1 ml/kg/day, in divided doses Fibers: partially hydrolyzed guar gum (PHGG), for children between 4-6 years: 3 g/day; 6-12 years: 4 g/day; and 12-16 years: 5 g/day. Treatment duration: 4 weeks In case of rectal impaction, an enema was given at the first visit. If persistent diarrhea was reported, the original dose was reduced by 50%. two groups were given an equal diet with fiber. However, as dietary fiber can bind fluid, the group given PHGG was recommended to increase their fluid intake.	Def: soft to formed stool consistency, absence of pain, stool withholding and blood in the stool, and no palpable rectal or abdominal mass. No data reported	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Lactulose as addition to PEG vs PEG alone					
Ala 2012	Age 1 – 12 years, N=200 , Rome III	Lactulose + PEG: lactulose max dose 3 cc/kg/day, twice daily, PEG maximum dose 0.7 g/kg /day, 13.8 - 40 g/day, twice daily.	Def: ≥ 3 bowel movements per week, ≤ 2 episodes of fecal incontinence per month without abdominal pain	Reported	NR

		PEG: maximum dose 0.7 g/kg /day, 13.8 - 40 g/day, twice daily. Treatment duration: 4 weeks In case of fecal impaction: disimpaction with suppository bisacodyl and then laxative therapy. Dietary advice given and toilet training discussed face to face and in pamphlets.	Time: 4 weeks		
Lactulose vs probiotics					
Lee 2022	Age 6 months – 10 years, N=187, Rome IV	Lactulose: 1.34 g/mL of lactulose. The starting dose was 1 mL/ kg/day, dosage change was allowed according to any clinical improvement noted during the follow-up period. Probiotic: Bioflor 250 mg powder containing 5 × 109 colony forming units of S. boulardii per sachet. Up to 2 years old, 2 sachets/day; > 2 years old, 3 sachets/day) Lactulose + probiotic: same as above. Treatment duration: 12 weeks All patients: glycerin enemas for disimpaction before the intervention. Drug changes were made when there was poor treatment	Def: ≥ 3 defecations per week (and in toilet-trained children, no incontinence episodes) Time: 12 weeks	Reported	Def: frequency per week, mean (SD) Time: 2 weeks

		outcome, poor compliance, and/or other side effects.			
Olgac 2013	Age 4 – 16 years, N=61, Rome III	Lactulose: 1 mL/kg/d Probiotic: 10^8 CFU L. reuteri DSM 17938 per day Treatment duration: 4 weeks Toilet training and dietary advice were given. Rescue medication: enema or MgO for no defecation >3 days	Not reported	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Magnesiumoxide (MgO) vs probiotics					
Bu 2007	Age 0 - 10 years. N=45, FC defined as 'stool frequency of <3 times per week for >2 months and at least one of the following minor criteria: anal fissures with bleeding due to constipation, fecal soiling, or passage of large and hard stool)'	MgO: 50mg/kg/d Probiotics: 8x10^8 CFU/d L. rhamnosus lcr35 Placebo: starch in content Treatment duration: 4 weeks Rescue medication: Lactulose (1mL/kg/d) if no defecation >3 days and glycerin enema if no defecation >5 days	Def: ≥ 3 spontaneous defecations per week with no episodes of fecal soiling in the fourth week. Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Kubota 2020	Age 6 months – 6 years, N=60, Rome IV	MgO + placebo: 30 mg/kg/day + lactose hydrate (placebo) Probiotics + placebo: 10^8 CFU L. reuteri DSM 17938 in 5 drops oil suspension + lactose hydrate MgO + probiotics: : 10^8 CFU L. reuteri DSM 17938 in 5 drops oil suspension twice a day + MgO (30mg/kg) plus lactose hydrate + lactulose hydrate	NR	Not reported	Def: change from baseline to endpoint as least square mean. Time: 4 weeks

		Treatment duration: 4 weeks Rescue medication: glycerin suppository for no defecation >3 days			
Liquid paraffin vs herbal medicine					
Mozaffarpur 2012	Age 4 – 13 years, N=81, Rome III	Liquid paraffin: ml/kg/day in 2 doses Herbal: cassia fistula emulsion 0.1 g/kg/day in 3 doses, adjusted to response Treatment duration: 3 weeks The treatments started with demystification. If any fecal mass was found, disimpaction was done with normal saline. Regular toilet sittings for 5 minutes after each meal and diet changes were recommended to all the children. Excluded when 'acceleration of constipation'.	Def: not fulfilling Rome III criteria anymore Time: 3 weeks	Reported	Def: frequency per week, mean (SD) Time: 3 weeks
Liquid paraffin vs synbiotics					
Khodadad 2010	Age 4 – 12 years, N=97, Rome III	Liquid paraffin: 1.5mL/kg/day Synbiotics: 1x10^9 CFU multispecies probiotic and fructo-oligosaccharides Treatment duration: 4 weeks Dietary and	Def: ≥3 BMs per week, ≤2 incontinence per month and no abdominal pain Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

		toilet training advice was given to all patients similarly. Toilet training consisted of sitting on the toilet 3 times per day for 5 minutes after each meal.			
Prucalopride vs placebo					
Mugie 2014	Age 6 months – 18 years, N=215, Rome III	Prucalopride: <50 kg 0.04 mg/kg once daily, >50 kg 2 mg tablet once daily Placebo: <50 kg 0.04 mg/kg once daily, >50 kg 2 mg tablet once daily If the child was <50 kg, dose could be increased to 0.06 mg/kg or decreased to 0.02 mg/kg after 4 weeks, based on treatment response and the presence of safety/ tolerability concerns. Treatment duration: 8 weeks Rescue therapy: no bowel movement for 3 or more consecutive days, 5 mg bisacodyl or 7.5 mg/mL sodium picosulfate droplets (1 droplet per 5 kg body mass) was allowed.	Def: mean spontaneous bowel movement frequency of 3 or more/week and a mean fecal incontinence frequency of 1 or less/2 weeks during weeks 5–8 of the double-blind period. Fecal incontinence was taken into account only after the acquisition of toileting skills. Time: 8 weeks	Reported	Def: frequency per week, change from baseline value to mean value across weeks 1-8, mean (SD) Time: 8 weeks
Lubiprostone vs placebo					
Benninga 2022	Age 6 – 17 years, N=606 , Rome III	Lubiprostone: <50 kg, doses of 12 micrograms twice/day. 50 kg or more, doses of 24 micrograms twice/day. Doses needed to be administered at least 5 hours apart	Def: overall Spontaneous Bowel Movement (SBM) response, defined as an increase of 1 or more SBM/wk compared with baseline and 3 or more SBMs/wk for at least	Reported	Def: see treatment success.

		with meals and more than 8 ounces (240 mL) of fluid. Placebo: same as above. Treatment duration: 12 weeks Dose could be increased to 24 microgram in patients who reported no treatment-related AEs and <3 SBMs after 1 week of treatment. Rescue therapy: prohibited during the first 24h after the first dose of study drug. After that it was allowed if no bowel movement was observed in the past 3 days. Study participants were instructed not to change their diet or lifestyle.	9 weeks, including 3 of the final 4 treatment weeks. Time: 12 weeks		
Linaclotide vs placebo					
Di Lorenzo 2020	Age 6 – 17 years, N=173, Rome III	Dose A: linaclotide 9 – 18 µg/day (depending on age) Dose B: linaclotide 18 – 36 µg/day (depending on age) Dose C: 36 – 72 µg/day (depending on age) Adult dose: linaclotide 145 µg (12-17 years old) Placebo: once/day Treatment duration: 4 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

Di Lorenzo 2024	Age 6 – 17 years, N=328, modified Rome III	Linaclotide: 72 µg once/day Placebo: once/day Treatment duration: 12 weeks Advice: dietary changes, adequate fluid intake, increased physical activity, and adequate time for bowel movements. Patients and caregivers were instructed to maintain them throughout the study Rescue therapy: permitted when at least 72 h had passed since the patient's previous bowel movement or when their symptoms became intolerable.	Def: proportion of participants who no longer fulfil modified Rome III criteria for functional constipation at the end of the study intervention period Time: 12 weeks	Reported	Def: frequency per week, mean (SD) Time: 12 weeks
Enemas as addition to PEG vs PEG alone					
Bongers 2009	Age 8 – 18 years, N=102, FC defined as 'presence of at least 2 of the 4 symptoms: spontaneous defecation frequency < 3 per week, fecal incontinence episodes ≥ 2 per week, passage of large-diameter stools that might obstruct the toilet, and palpable abdominal or rectal mass on physical examination'	Enema + PEG: 120 ml sodium-dioctyl sulfosuccinate and sorbitol 3 times/week during the first 3 months. Frequency then reduced by one enema per week very three months. PEG: starting dose of 0.5 g/kg/day. Insufficient treatment, dose increased to a max of 1.5 g/kg. A rectal enema or bisacodyl suppository of 5 mg was only prescribed in case of reoccurrence of fecal impaction (control group only).	Def: 3 or more bowel movements per week, and less than 1 incontinence episode per week, irrespective of laxative use Time: 52 weeks	Reported	Def: frequency per week, mean. No SD reported. Time: 52 weeks

		Education and behavioral strategies were given in both groups. Treatment duration: 52 weeks			
Domperidone as addition to PEG vs PEG alone					
Dehghani 2014	Age 0 – 12 years, N=105, Rome III	Intervention: domperidone syrup 0.15 mL/kg three times a day for 3 months + PEG: 0.6 g/kg/day two times a day for 6 months Control: PEG 0.6 g/kg/day two times a day for 6 months + placebo with the same color, taste, and smell as domperidone with the same dose (as syrup) for 3 months. Treatment duration: 6 months	Def: not meeting Rome III criteria Time: 6 months	Reported	Def: number of patients that reported ≥ 3 episodes of defecation per week Time: 6 months

AE: adverse events, FC: functional constipaiton

Appendix 3. Studiekarakteristieken niet-medicamenteuze behandeling

Study ID	**Participants**	**Intervention** (comparison, dosage, treatment period, concomitant therapy)	**Treatment success** (definition + time of measurement)	**Withdrawals due to AE reported?**	**Defecation frequency**
Cow's milk free diet vs normal diet					
Dehghani 2012	Age 0 – 14 years, N=140, Rome III	Intervention: Cow's milk free diet Control: Cow's milk diet Treatment duration: 4 weeks	Def: not meeting Rome III criteria Time: 4 weeks	Reported	Def: number of patients with 3 or more defecations per week Time: 4 weeks
Iacono 1998	Age 0 – 6 years, N=65, FC defined as 'chronic fecal retention (one bowel movement every 3 to 15 days), often associated with abdominal symptoms (abdominal pain, painful defecation, and so forth).	Intervention: soy-milk 5-10L over 2 weeks Control: cow's milk 5-10L over 2 weeks Treatment duration: 2 weeks pre cross-over, 1 week was-out before cross-over, 2 weeks post cross-over Rescue therapy: no response to the soy-milk diet, high doses of laxatives	NR	Reported	Def: number of bowel movements per 2 weeks, median (IQR) Time: 2 weeks Not reported pre crossover
Formula hydrolyzed whey + prebiotics vs Formula cow's milk protein + prebiotics					
Fabrizio 2022	Age 28 – 300 days, N=100, FC defined as 'at least two grade 1 stools (using 5-point stool consistency	Intervention: formula consisting of hydrolyzed cow's milk protein and prebiotic blend (polydextrose	NR	Reported	Def: frequency per day, mean (SE) Time: 2 weeks

	scale where; hard =1, formed =2, mushy =3, unformed or seedy =4, watery =5) over the last 10-day period OR two or more stools of a minimum grade 2 consistency (using the 5-point stool consistency scale) AND 48 consecutive hours without a bowel movement over the last 10-day period'	and galactooligosaccharide) Control: normal formula based on cow's milk and prebiotic blend (polydextrose and galactooligosaccharide) Treatment duration: 2 weeks Concurrent therapy: laxatives were not prohibited. Oral laxatives (Intervention: n=1, Control: n=1). Rectal stimulation or suppository (Intervention: n=2, Control: n=2)			
Addition of cow's milk free diet to laxative treatment					
Bourkheili 2021	Age 4 – 14 years, N=71, Rome III	Intervention: cow's milk-free and dairy-free diet plus 30 mg/kg/day of calcium syrup (Calciram, Ramo Pharmin Company, IR Iran) for four consecutive weeks Control: no restrictions in consuming cow's milk and dairy products Both groups: PEG 1g/kg/day for four weeks and high-fiber foods Treatment duration: 4 weeks	Def: not meeting the Rome III criteria Time: 4 weeks	Reported	Def: number of patients with 2 or less defecations per week Time: 4 weeks

Fiber vs placebo					
Chmielewska 2011	Age 3 – 16 years, N=80, Rome III	Intervention: glucomannan 2.52 g/day Control: placebo (maltodextrin, 2.52 g/d) Treatment duration: 4 weeks Concomitant therapy: 58% was on laxatives during study	Def: ≥3 bowel movements with no episodes of soiling during the last week Time: 4 weeks	Reported	Def: bowel movements per week, median (IQR) Time: 4 weeks
Weber 2014	Age 4 – 12 years, N=57, Rome III	Intervention: fiber mixture (fructo-oligosaccharides, inulin, gum Arabic, resistant starch, soy polysaccharide and cellulose) Control: placebo (maltodextrin, 3.8g/d <18kg bw, 7.6g/d >18kg bw)	Def: a patient maintaining normal bowel habits without the use of stool softeners or enemas. Time: 4 weeks	Reported	Def: bowel movements per day, mean (SD) Time: 4 weeks
Loening-Baucke 2004	Age 4 – 12 years, N=46, Rome III	Intervention: glucomannan 100 mg/kg/day, max 5 g/day and rounded to the nearest 500mg Control: placebo (maltodextrin) Treatment duration: 4 weeks and 4 more weeks after cross-over (no washout) All patients received toilet training.	Def: ≥3 BMs/wk and ≤1 soiling episode/3 wk with no abdominal pain, rated by physician Time: 8 weeks No data reported pre cross-over	Reported	Def: frequency of bowel movements per week, mean (SD) Time: 8 weeks No data reported pre cross-over

Fiber vs laxatives					
Cassetari 2018	Age 5 – 10, N=80, Rome IV	PEG 3350 + electrolytes: dosage NR Sodium picosulfate: dosage NR Green banana biomass (GBB): 30 g per day PEG + GBB: unclear Sodium picosulfate + GBB: unclear Treatment duration: 8 weeks Concomitant therapy: dietary advice	NR	NR	Def: number of patients having more than 3 bowel motions per week. Time: after 8 weeks
Kokke 2008	Age 1 – 13 years, N=135, FC defined as 2 of 4 criteria: stool frequency less than 3 times per week, fecal incontinence 2 or more times per week, periodic passage of large amounts of stool at least once every 7 to 30 days, or a palpable abdominal or rectal mass	Intervention: fiber mixture: 10 g/125 mL Control: lactulose 10 g/125 mL Patients with a weight <15 kg received 1 bottle (125 mL, 10 g fibers) daily, those with a weight between 15 kg and 20 kg received 2 bottles (250 mL, 20 g) daily, and those with a weight above 20 kg received 3 bottles (375 mL, 30 g) daily. The study product was taken at breakfast and, in the case of 2 or more bottles, also at lunch.	NR	Reported	Def: frequency per week. Unclear if median/mean. No measure of spread reported.

		Treatment duration: 8 weeks + 4 weeks weaning period. Total of 12 weeks. Enema was given in case of rectal impaction before start treatment. Rescue medication: macrogol 3350 in no improvement after 3 weeks. If persistent diarrhea was reported, the original dose was reduced by 50%.			
Quitadamo 2012	Age 4 – 10 years, N=100, Rome III	Intervention: Fiber mixture: 16,8 g per day, increase up to 22,4 g per day if necessary Control: PEG 3350 + electrolytes: 0,5 g/kg per day, increase up to 1.0 g/kg per day if necessary Treatment duration: 8 weeks Concomitant therapy: disimpaction before start treatment. Rescue therapy: enemas if no defecation for > 3 days	Def: 3 or more bowel movements per week, 2 or higher stool consistency grade on BSFS, absence of fecal incontinence, abdominal pain, pain on defecation, and fecal bleeding. Time: 8 weeks	Reported	Def: Per week, mean (SD) Time: 8 weeks
Üstündağ 2010	Age 4 – 16 years, N=68, Rome III	Intervention: partially hydrolyzed guar gum (PHGG), for children between 4-6 years: 3 g/day; 6-12 years: 4 g/day; and 12-16	Def: soft to formed stool consistency, absence of pain, stool withholding and blood in the stool,	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

		years: 5 g/day. Control: lactulose: 1 ml/kg/day, in divided doses Treatment duration: 4 weeks In case of rectal impaction, an enema was given at the first visit. If persistent diarrhea was reported, the original dose was reduced by 50%. two groups were given an equal diet with fiber. However, as dietary fiber can bind fluid, the group given PHGG was recommended to increase their fluid intake.	and no palpable rectal or abdominal mass. No data reported		
Increased fluid intake vs control					
Young 1998	Age 2 – 12 years, N=108, FC defined as 'simple constipation of a moderate to severe degree as determined by a Constipation Assessment Scale score of 8 or greater'	Intervention: increased water intake Intervention: increased hyperosmolar liquid intake Control: control Treatment duration: 3 weeks	NR	NR	Def: frequency per week, mean No SD reported Time: 3 weeks
Probiotics vs placebo					
Bu 2007	Age 0 – 10 years, N=45, FC defined as 'stool frequency of <3 times per week for >2	Intervention: 8x10^8 CFU/d *L. casei rhamnosus* lcr35 Control 1: magnesium oxide	Def: ≥ 3 spontaneous defecations per week with no episodes of	Reported	Def: frequency per week, mean (SD)

	months and at least one of the following minor criteria: anal fissures with bleeding due to constipation, fecal soiling, or passage of large and hard stool.	50mg/kg/d Control 2: placebo (starch) Treatment duration: 4 weeks Rescue therapy: lactulose (1mL/kg/d) if no defecation >3 days and glycerin enema if no defecation >5 days	fecal soiling in the fourth week. Time: 4 weeks		Time: 4 weeks
Coccorullo 2010	Age 6 months – 18 years, N=44, Rome III	Intervention: 10^8 CFU *L. reuteri* DSM 17938 in 5 drops oil suspension Control: placebo in 5 drops oil suspension Treatment duration: 8 weeks Rescue therapy: glycerin suppository for no defecation >5 days	Def: ≥3 defecations per week Time: 8 weeks	Reported	Def: frequency per day Unclear if mean or median and no spread reported Time: 8 weeks
Gan 2022	Age 4 – 12 years, N=100, Rome III	Intervention: probiotic chewable tablets twice/day containing *L. acidophilus DDS-1^{R} and B. Lactis UABla-12^{TM}* 5 × 109 CFU/tablet Control: chewable placebo tablet twice/day Treatment duration: 4 weeks	NR	Reported	Def: frequency per week, mean No SD reported Time: 4 weeks
Lojanatorn 2023	Age 1 – 5 years old, N=39, Rome IV	Intervention: B. clausii 2 billion spores in 5 mL once/day Control: placebo once/day	Def: at least 3 defecations per week and stool consistency at	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

		Treatment duration: 4 weeks Rescue therapy: sodium chloride enema once if the child did not defecate for three or more consecutive days (10 mL for children aged 1-2 years, and 20 mL for children aged 3-5 years) Both groups: caregivers were educated on appropriate fiber and fluid intake, toilet training in developmentally appropriate normal children aged >2-3 years	least grade 3 on the Bristol stool chart Time: 4 weeks		
Tabbers 2011	Age 3 – 16 years, N=154, Rome III	Intervention: Activia (125g pet pot) with *B. lactis* DN-173 010 at least 4,25*10^9 CFU and yoghurt starter cultures 2 pots per day Control: milk-based, nonfermented dairy product (125 g per pot) 2 pots per day Treatment duration: 3 weeks Concomitant therapy: no treatment for FC <2 weeks before start of the study	Def: 3 or more bowel movements per week and <1 fecal incontinence episode in 2 weeks over the last 2 weeks of product consumption Time: 3 weeks	Reported	Def: increase in bowel movements per week from baseline to week 3, mean (SD) Time: 3 weeks
Tjokronegoro 2020	Age 4 – 10 years, N=78, Rome III	Intervention: *L. acidophilus, B. longum, and S. thermophylus* 1× 109cfu/day	Def: overall improvement was defined as decreased	Reported	Def: frequency per week, mean (SD)

		twice/day Control: placebo (maltodextrin) twice/day Treatment duration: 4 weeks Both groups: disimpaction with bisacodyl suppositories twice before start treatment	constipation severity score >60% at the end of evaluation. Time: 4 weeks		Time: 4 weeks
Wojtyniak 2017	Age 0 – 5 years, N=94, Rome III	Intervention: *L. rhamnosus* Lcr35 8 × 10^8 CFU Control: placebo (milk powder and 1% magnesium stearate) Treatment duration: 4 weeks Rescue therapy: PEG 1.5mg/kg/d as single dose for no defecation >3 days	Def: ≥3 spontaneous stools per week, without episodes of fecal soiling (in toilet-trained children), in the last week of the intervention Time: 4 weeks	Reported	Def: frequency per week, median (IQR) Time: 4 weeks
Zaja 2021	Age 10 – 18 years, N=31, Rome IV* *All included patients had anorexia nervosa and were female	Intervention: *L. reuteri* DSM17938 108 CFU twice daily as chewable tablet Control: placebo Treatment duration: 3 months Rescue therapy: glycerin suppository if no defecation for > 5 days Both groups: conventional nutritional intervention, consisting of serving normal	Def: relief of constipation, defined as a drop-out from Rome-IV criteria Time: 3 months	Reported	Def: frequency per week, mean and median Unclear if range is IQR or normal range. Time: 6 months

		food under the supervision of nurses that calculated the daily caloric intake through 5-6 meals, and additional enteral nutrition (standard polymeric enteral formula)			
Probiotics vs laxatives					
Lee 2022	Age 6 months – 10 years, N=187, Rome IV	Probiotics: 5 × 109 CFU *S. boulardii* per sachet was used. Up to 2 years old, 2 sachets/day; over 2 years old, 3 sachets/day. Dosage was not adjusted according to clinical outcomes. Laxative only: lactulose (1.34 g/mL), 1 mL/ kg/day. Dosage change was allowed according to any clinical improvement. Probiotics + laxative: 5 × 109 CFU *S. boulardii* + lactulose 1 mL/kg/day. Treatment duration: 12 weeks Both groups: glycerin enemas for disimpaction before the intervention Drug changes were made when there was poor treatment outcome, poor compliance, and/or other	Def: ≥ 3 defecations per week (and in toilet-trained children, no incontinence episodes) Time: 12 weeks	Reported	Def: frequency per week, mean (SD) Time: 12 weeks

		side effects. Patients were then counted as withdrawals.			
Olgaç 2013	Age 4 – 16 years. N=61, Rome III	Intervention: 10^8 *CFU L. reuteri* DSM 17938 Laxative: lactulose 1 mL/kg/d Treatment duration: 4 weeks Both groups received toilet training and dietary advice. Rescue therapy: enema or MgO for no defecation >3 days	NR	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Probiotics as addition to laxatives					
Abediny 2016	Age 4 – 12 years, N=90, Rome III	Intervention: *multispecies probiotic* + PEG4000 (0.7-1.5 g/kg/d) Control: PEG4000 (0.7-1.5 g/kg/d) Treatment duration: 4 weeks	NR	NR	Def: frequency per week No data reported.
Banaszkiewicz 2005	Age 2 – 16 years, N=84, FC defined as '<3 BMs per week for at least 12 weeks'	Intervention: 10^9 CFU of *Lacticaseibacillus rhamnosus* plus 1 mL/kg/day of 70% lactulose Control: placebo plus 1 mL/kg/day of 70% lactulose Treatment duration: 12 weeks	Def: ≥3 spontaneous BMs per week with no episodes of fecal soiling Time: 12 weeks	Reported	Def: frequency per week, mean (SD) Time: 12 weeks

		Both groups: rectal disimpaction before start of intervention			
Foroughi 2022	Age 2 – 12 years, N=144, Rome IV	Group 1: PEG 6 g/day Group 2: PEG 6 g/day + 109 CFU *mixture of probiotics* (Lactobacillus reuteri, Lactobacillus rhamnosus, and Bifidobacterium infantis) Group 3: psyllium (seen as prebiotics) Group 4: psyllium + probiotics mixture Treatment duration: 3 weeks Both groups: Dietary advice and toilet training were provided	NR	NR	Def: frequency per week, mean (SD) Time: 3 weeks
Jadrešin 2018	Age 2 – 16 years, N=33, Rome III	Intervention: 10^8 CFU *L. reuteri* DSM 17938 plus lactulose 1-3ml/kg/d. Control: placebo plus lactulose 1-3ml/kg/d Treatment duration: 12 weeks	Def: absence of symptoms at the end of study Time: 12 weeks	Reported	Def: frequency No data reported Time: 12 weeks
Kubota 2020	Age 6 months – 6 years, N=60, Rome IV	Probiotics: 10^8 CFU *L. reuteri* DSM 17938 in 5 drops oil suspension twice a day plus lactose hydrate Laxative: MgO (30mg/kg) and lactose hydrate only	NR	NR per group	Def: change from baseline to endpoint, least square mean (95% CI)

		Probiotics + Laxative: 10^8 CFU *L. reuteri* DSM 17938 in 5 drops oil suspension twice a day plus MgO (30mg/kg) plus lactose hydrate Treatment duration: 4 weeks Rescue therapy: glycerin suppository for no defecation >3 days			
Russo 2017	Age 4 – 12 years, N=55, Rome III	Intervention: probiotic mixture (3 strains of *bifidobacteria*) plus PEG4000 0.4-0.8 g/kg/d Control: PEG4000 0.4-0.8 g/kg/d Treatment duration: 8 weeks Both groups: toilet training Rescue therapy: enema for no defecation >3 days	Def: ≥3 defecation per week, stool consistency ≥ grade 3 on BSFS, and no episodes of abdominal pain, fecal incontinence, painful defecation, and rectal bleeding Time: 8 weeks	Reported	Def: frequency per week, mean (SD) Time: 8 weeks
Wegner 2018	Age 3 – 7 years, N=129, Rome III	Intervention: 10^8 CFU *L. reuteri* DSM 17938 plus 10g/d PEG Control: placebo plus 10g/d PEG Treatment duration: 8 weeks Rescue therapy: enema after 5 days without defecation	NR	Reported	Def: frequency per week, mean (SD) Time: 8 weeks

Sadeghzadeh 2014	Age 4 – 12 years, N=56, Rome III	Intervention: *multispecies probiotic* of 7 strains plus lactulose (1 mL/kg/d) Control: placebo plus lactulose (1 mL/kg/d) Treatment duration: 4 weeks	NR	Reported	Def: comparison bowel movements between beginning and end of 4th week. Unclear if per week/per day, or if its increase in defecation Time: 4 weeks
Probiotics as addition to a goat yoghurt					
Guerra 2011	Age 5 – 15 years, N=60, Rome III	Intervention: goat yogurt supplemented with 10^ 9 CFU/mL *B. longum* daily Control: goat yogurt only (with classical yogurt starters, *Lactobacillus delbrueckii subspecies bulgaricus* and *Streptococcus thermophilus*) Treatment duration: 5 weeks	NR	Reported	Def: grouped per category (≤2, 3-6, ≥7 bowel movements per week) Time: Grouped per category (≤2, 3-6, ≥7 BM's)/wk Time: 5 weeks No data reported, only with figure.
Formula intact protein + probiotic + PEG vs Formula hydrolyzed whey protein + PEG					
Sevilla 2022	Age 12 – 32 months, N=96, Rome III	Intervention: Test formula (Friso Comfort Next) consisted of intact protein, 20% milk fat, a fibre mixture of galacto-oligosaccharides (GOS), inulin and carob bean gum (CBG), 100% lactose and a probiotic (B. lactis HN019). Three times a day.	Def: meeting less than 2 of the Rome III criteria (inverted from paper: data were presented as patients still fulfilling Rome criteria) Time: 8 weeks	Reported	Def: frequency per week, mean (SD) Time: 8 weeks

		Control: control formula (Similac Comfort) consisted of partially hydrolysed whey (pHW), 2'-fucosyl- lactose (2'-FL) and reduced lactose compared to the test formula. Three times a day. Treatment duration: 8 weeks Concurrent therapy both groups: disimpaction with PEG3350 1.5 g/kg/day and PEG3350 during first 4 weeks. First 2 weeks 0.4 g/kg/day, last 2 weeks 0.8 g/kg/day			
Prebiotics vs placebo					
Da Silva Souza 2018	Age 6 – 24 months, N=38, FC defined as 'the elimination of hard stools associated with one of the following characteristics: pain or straining while passing stools, scybalous stools, cylindrical and cracked or cylindrical and thick stools and stool frequency less than three times per week'	Intervention: fructo-oligosaccharides, dosage of 6, 9, or 12 g/d based on weight groups of 6.0–8.9 kg, 9.0–11.9 kg or over 12.0 kg, respectively Placebo: maltodextrin, 6, 9, or 12 g/d same weight groups Treatment duration: 4 weeks	Def: a normal bowel pattern at the end of the study, i.e., predominantly soft, amorphous or cylindrical stools without cracks as well as the absence of pain or difficulty passing stools Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Prebiotics vs laxatives (and with addition of probiotics)					

Foroughi 2022	Age 2 – 12 years, N=144, Rome IV	Group 1 (Prebiotics): Psyllium Seed Husk Powder 6 g per day Group 2 (Laxative): PEG 6 g per day Group 3 (Laxative + probiotics): 6 g per day + 109 CFU bacterial probiotics (mixture of different stems) Group 4 (Prebioitcs + probiotics): Psyllium Seed Husk Powder 6 g per day day + 109 CFU bac- terial probiotics (mixture of different stems) Concomitant therapy: dietary advice and toilet training were provided to all parents.	NR	NR	Def: frequency per week, mean (SD) Time: 3 weeks
Formula with prebiotics and hydrolyzed whey protein vs standard formula					
Bongers 2007	Age 3 – 20 weeks, N=38, FC defined as 'at least one of the following symptoms: defecation frequency < 3/week; painful defecation; abdominal or rectal palpable mass	Intervention: infant formula (Omneo/Conformil), mix of prebiotic fibres (galacto-oligosaccharides and long chain fructo-oligosaccharides), sn-2 palmitic acid and hydrolyzed whey protein Control: standard formula Treatment duration: 3 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 3 weeks

Savino 2005	Age 0 – 16 weeks, N=123, FC defined as 'stool frequency of less than 1 stool a day'	Intervention: infant formula (Omneo/Conformil), mix of prebiotic fibres, (galacto-oligosaccharides and long chain fructo-oligosaccharides), sn-2 palmitic acid and hydrolyzed whey protein Control: standard formula Treatment duration: 2 weeks	NR	Reported	Def: frequency per day, mean (SD) Time: 2 weeks
Synbiotics vs placebo					
Baştürk 2017	Age 4 – 18 years, N=155, Rome III	Intervention: synbiotics of 4 strains at 4*10^9 CFU and prebiotic mix Control: placebo Treatment duration: 4 weeks Both groups: received toilet training and dietary advice. Rescue therapy: fleet enema (paraffin oil 15-30 mL/y)	Def: complete benefit by resolution of all complaints of the patients (weekly number of defecation ≥ 3, softening in the stool consistency (Bristol ≥ 4 points), and weekly encopresis ≤ 1) Time: 4 weeks	Reported	Def: Number of patients with >3 stools per week Time: 4 weeks
Synbiotics vs laxative					
Khodadad 2010	Age 4 – 12 years, N=97, Rome III	Group 1 (Synbiotics): 1x10^9 CFU multispecies probiotic and fructo-oligosaccharides Group 2 (Laxative): Liquid paraffin 1.5 mL/kg/day Group 3 (Synbiotics + laxative): 1x10^9 CFU multispecies probiotic and	Def: ≥3 BMs per week, ≤2 incontinence per month and no abdominal pain Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks

		fructo-oligosaccharides + Liquid paraffin 1.5 mL/kg/day Treatment duration: 4 weeks Dietary and toilet training advice was given to all patients similarly. Toilet training consisted of sitting on the toilet 3 times per day for 5 minutes after each meal.			
Behavioral therapy as addition to conventional laxative treatment					
Van Dijk 2008	Age 4 – 18 years, N=134, FC defined as '2 of 4 criteria: defecation frequency < 3 times per week, fecal incontinence ≥ 2 times per week, passage of large amounts of stool at least once every 7 to 30 days (large enough to clog the toilet), or a palpable abdominal or rectal fecal mass	Intervention: behavioral therapy (12 visits in 22 weeks) + conventional pharmacological therapy as the control group Control: disimpaction with enemas at start, maintenance PEG3350 1-2 sachet/day (1 sachet 10 g) and if necessary enema or bisacodyl suppositories, same FU sessions. Both groups: received toilet training	Def: ≥3 BM/week and ≤ 1 episodes of fecal incontinence per 2 weeks irrespective of laxative use. Time: 22 weeks	Reported	Def: frequency per week, mean (95% CI) Time: 22 weeks

		Rescue therapy: enema of suppository if no defecation > 3 day			
Biofeedback as addition to conventional laxative treatment					
Loening-Baucke 1990	Age 5 – 16 years old, N=43, FC defined as '≥2 soiling episodes per week, evidence of a huge amount of fecal material in the rectal ampulla at rectal examination, and abnormal defecation (abnormal contraction of the external anal sphincter and pelvic floor during defecation attempts)'	Intervention: Addition of biofeedback (2-6 weekly sessions) to magnesiumhydroxide. Control: disimpaction + magnesiumhydroxide (dose adjusted to have daily bowel movement without soiling) Treatment duration: 6 months Both groups: received toilet training	Def: ≥3 bowel movements per week and ≤2 soiling episodes per month while not receiving laxatives for 4 weeks Time: 7 months	Reported	NR
Sunic-Omejc 2002	Age 5 – 15 years, N=49, FC defined as 'meet at least two of the following criteria: defecation frequency less than 3 times per week, two or more episodes of soiling and/or encopresis per week, periodic evacuation of large volume stools, at least once every 7 – 10 days, and palpable abdominal rectal mass'	Intervention: addition of biofeedback (1 session + home exercises) to lactulose. Control: lactulose with dose titration and weekly follow-up Treatment duration: 12 weeks Both groups: received toilet training and dietary advice for high fiber diet	Def: ≥3 bowel movements per week and ≤2 soiling episodes per month without laxatives Time: 12 weeks	Reported	NR

		Rescue therapy: enema if no defecation for more than 3 days.			
Van der Plas 1996	Age 5 – 16 years, N=192, FC defined as 'two of these four criteria: stool frequency less than three per week, two or more soiling and/or encopresis episodes per week, periodic passage of very large amounts of stool at least once every 7–30 days, or a palpable abdominal or rectal mass'	Intervention: addition of biofeedback (5 sessions) to lactitol. Control: first disimpcation with 3-7 days enema. Maintenance treatment with lactitol betagalactoside sorbitol and weekly FU Treatment duration: 6 weeks	Def: ≥3 bowel movements per week and ≤2 soiling episodes per month while not receiving laxatives for 4 weeks Time: 6 weeks	Reported	NR
Biofeedback vs no biofeedback					
Castilla 2021 (abstract only)	Age range unclear. Median age (IQR) 10.5 (6), N=25, Rome IV with no response to pharmacological therapy (for more than two years)	Intervention: biofeedback - no further detail provided, apart from that 10 sessions (mean) were delivered per patient Control: no biofeedback. No further information.	Def: ≥3 bowel movements per week and ≤2 soiling episodes per month while not receiving laxatives for 4 weeks Time: unclear	NR	NR
Biofeedback at home + in laboratory vs biofeedback in laboratory					
Croffie 2005	Age 6 – 14 years, N=36, FC defined as 'defined as less than 3 bowel movements	Intervention: addition of biofeedback at home daily with portable EMG to	Def: ≥3 bowel movements per week with no discomfort and	NR	Def: number of bowel movements per week, mean. Unclear if SD or SE.

	per week, with or without overflow incontinence, and not improving, despite compliance with conventional therapy, including laxative and toilet behavior modification, for at least 6 months'	biofeedback in laboratory. Control: biofeedback in laboratory (5 sessions at 2-week intervals). Treatment duration: 10 weeks, outcome assessment 8 weeks later. Concomitant medication: laxatives were continued, weaned after last session Both groups: toilet training was previously advised.	<2 soiling episodes per month, and no, or only rare use of laxatives. Time: 4 months		Time: 4 months
Pelvic physiotherapy + standard medical care vs standard medical care					
Van Engelenburg 2017	Age 5 – 15 years, N=53, Rome III	Intervention: addition of pelvic floor physiotherapy (max 6 sessions in 6 months) to standard medical care Control: standard medical care including education, demystification, dietary advice, toilet training, keeping track of bladder and bowel diaries, and when needed prescription of PEG (PEG 0.3–0.8 g/kg body weight per day). Treatment duration: 6 months Concomitant: both groups received disimpaction with	Def: absence of FC according to the 6 Rome III criteria, irrespective of PEG use Time: 6 months	Reported	Def: number of patients with 3 or more bowel movements per week (of the patients who had <3 bowel movements per week at baseline) Time: 6 months

		high dose PEG if large fecal mass was present at intake (rectal examination was performed to confirm or exclude FC when only 1 Rome III criterion was met)			
Abdominal muscle training/breathing exercises/abdominal massage + laxative vs laxative					
Silva 2013	Age 4 - 18 years, N=72, Rome III	Intervention: addition of physiotherapy: isometric training of the abdominal muscles, diaphragmatic breathing exercises and abdominal massage (twice weekly sessions). Control: disimpaction with enema 1-5 days, maintenance magnesium hydroxide Treatment duration: 6 weeks Both groups: received toilet training and dietary advice on high fiber intake and water intake Rescue therapy: enema if needed	NR	Reported	Def: number of days per week with defecation, mean (SD) Time: 6 weeks
Manual therapy vs laxative					
Blanco Diaz 2020	Age 2 – 14 years, N=47, Rome III	Intervention: manual physical therapy performed by a physiotherapist. Nine 30	NR	NR	Def: frequency per week, median (IQR)

		minute sessions, weekly in the first two months, biweekly in the third month. Control: PEG (0.5 g/kg/day, range 0.2–0.8) 2 months until obtaining a regular defecation habit and followed by a phase of medication withdrawal. Treatment duration: 3 months Concurrent therapy in both groups: Both groups(all patients): (1) 3 days disimpaction with PEG (1-1.5g/kg/day in 2 doses), (2) behavioral management consisting of modification of defacatory habits, establishing routine of visiting bathroom after meals, (3) diet rich in fibers and generous liquid intake			Time: 3 months
Abdominal transcutaneous electrical stimulation vs sham therapy					
Clarke 2009	Age 7 – 18 year, N=33, Rome II	Intervention: 12x20 minutes session of abdominal interferential electrical stimulation Control: sham stimulation Treatment duration: 4 weeks	NR	NR	NR

		Concomitant therapy: there was medication use in 26/33 children			
Parasacral nerve stimulation vs sham therapy					
De Abreu 2021	Age 5 – 17 years, N=40, Rome IV	Intervention: standard urotherapy + parasacral nerve stimulation (20 minute session, 3 times a week, 20 sessions in total) Control: standard urotherapy + sham parasacral nerve stimulation Treatment duration: 7 weeks Both groups: toilet training and dietary advice on fiber rich foods	Def: Number of patients without FC according to Rome IV after treatment Time: 7-9 weeks	Reported	Def: number of patients with less than two bowel movements per week Time: 7-9 weeks
Abdominal electrical stimulation + pelvic floor muscle exercises (PFME) vs pelvic floor muscle exercises					
Ladi-Seyedian 2020	Age 5 – 13 years, N=34, Rome IV	Intervention: abdominal interferential electrical stimulation (twice weekly, 5 weeks) and pelvic floor muscle exercises Control: pelvic floor muscle exercises (same sessions). Treatment duration: 5 weeks Concomitant therapy: mild laxatives were advised if	Def: number of patients not fulfilling Rome IV criteria Time: 6 months	Reported	Def: number of bowel movements, mean (SD) Time: 6 months

		refractory to diet intervention Both groups: received toilet training and dietary advice			
Sharifi-Rad 2018	Age 5 – 13 years, N=90, Rome III	Intervention: abdominal interferential electrical stimulation (twice weekly, 5 weeks) and pelvic floor muscle exercises Control: sham stimulation and pelvic floor muscle exercises Treatment duration: 5 weeks Concomitant therapy: PEG if necessary.	Def: number of patients not fulfilling Rome III criteria Time: 6 months	Reported	Def: Number of bowel movements, median (IQR) Time: 6 months
Abdominal electrical stimulation + standard therapy vs standard therapy					
Khan 2020	Age 3 – 15 years, N=80, Rome IV	Group 1: Addition of abdominal cryotherapy (-10 °C) 6-10 minutes daily for 10 sessions Group 2: Addition of abdominal percutaneous electroneuro-stimulation 6-10 minutes daily for 10 sessions Group 3: Addition of abdominal cryotherapy and percutaneous electroneuro-stimulation Group 4: standard therapy:	Def: independent stools and no encopresis Time: unlcear	NR	NR

		laxatives, diet, probiotics, choleretic drugs, enzymes Treatment duration: 10 days			
Tibial nerve stimulation + pelvic floor muscle exercises vs pelvic floor muscle exercises (PFME)					
Yu 2023	Age 4 – 14 years, N=82, Rome IV	Intervention: percutaneous Tibial Nerve Stimulation (PTNS) with (PFE) twice daily for 4 weeks. Control: Sham PTNS + PFE. PFE was performed using an electromyography biofeedback method, in which an electrode is inserted through the anus. 20-40 hours of progressive resistance training. These hours would be best spread over 4 weeks, with 15 minutes of exercises twice per day. Treatment duration: 4 weeks	Def: Full remission was defined as SBM ≥3 per week along with most or all secondary outcomes recovered. Improvement was defined as SBM ≥3 per week with at least 1 secondary outcome recovered. Time: 16 weeks (4 weeks treatment, 12 weeks follow-up)	Reported	Def: changes in spontaneous bowel movements per week from baseline, mean (95% CI)
Herbal medicine vs laxative					
Dehghani 2019	Age 4 – 12 years, N=92, Rome III	Intervention: Black Strap Molasses syrup (40%w/v) 1 mL/kg body weight/day Laxative: PEG syrup (40% w/v) 1 mL/kg body weight/day Treatment duration: 4 weeks	Def: not fulfilling the Rome III criteria Time: 4 weeks	Reported	Def: number of patients with ≤2 BM/week Time: 4 weeks

		Concomitant therapy: toilet training and nutritional advice in both groups.			
Esmaeilidooki 2016	Age 2 – 15 years, N=109, Rome III	Intervetion: Cassia Fistula's Emulsion 1 cc/kg per day Laxative: PEG 4000: 0.7 – 0.8 g/kg per day Treatment duration: 4 weeks	Def: No longer fulfilling Rome III criteria Time: 4 weeks	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Nasri 2022	Age 2 – 15 years, N=120, Rome IV	Intervention: LaxaPlus Barij® 1 mL/kg daily divided into three doses for <30 kg, 10 mL three times daily for >30 kg Laxative: PEG 4000 0.7 g/kg three times per day Treatment duration: 8 weeks	NR	Reported	Def: frequency, unclear if per day or per week, mean (SD) Time: 8 weeks
Imanieh 2022	Age 1 – 18 years, N=100, Rome IV	Intervention: R. damascene and brown sugar syrup: 0.1g damask rose petals and 0.85g brown sugar per 1 mL solution. Initial dosage was 1 ml/kg per day. Laxative: PEG initial dosage was 1 ml/kg per day. Both groups: If no response, the dosage was increased to 2 ml/kg. Treatment duration: 4 weeks	Def: having fewer than two of the ROME IV criteria after treatment Time: 4 weeks	Reported	Def: number of patients with 2 or fewer defecations per week Time: 4 weeks

Nimrouzi 2015	Age 2 – 12, N=120, Rome III	Intervention: D. Sophia seed 2 g for 2-4 years old, 3 g for 4-12 years old Laxative: PEG 4000 0.4 g/kg per day Treatment duration: 8 weeks	Def: Improvement of constipation for at least 3 bowel movements, soft stool and convenient defecation, no soiling and bloody stool per week as well as exiting the Rome III criteria for constipation after the third week. Time: 8 weeks	Reported	Def: frequency per week, median (IQR) Time: 3 weeks
Saneian 2021	Age 2 – 15 years, N=60, Rome IV	Intervention: Golghand® 0.5 g/kg per day Laxative: PEG 4000 0.7 g/kg per day Treatment duration: 8 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 8 weeks
Tavassoli 2021	Age 4 – 10 years, N=140, Rome III	Intervention: Viola Flower Syrup: 5 cc 3 times per day Laxative: PEG 1 g/kg per day Treatment duration: 4 weeks	NR	Reported	Def: frequency per week, mean (SD) Time: 4 weeks
Mozaffarpur 2012	Age 4 – 13 years, N=81, Rome III	Intervention: cassia fistula emulsion 0.1 g/kg/day in 3 doses, adjusted to response Laxative: liquid paraffin ml/kg/day in 2 doses Treatment duration: 3 weeks The treatments started with demystification. If any fecal mass was found,	Def: not fulfilling Rome III criteria anymore Time: 3 weeks	Reported	Def: frequency per week, mean (SD) Time: 3 weeks

		disimpaction was done with normal saline. Regular toilet sittings for 5 minutes after each meal and diet changes were recommended to all the children. Excluded when 'acceleration of constipation'.			
Herbal vs placebo					
Cai 2018	Age 1 – 14 years, N=480, adjusted Rome IV and food retention syndrome (in traditional Chinese medicine)	Intervention: Xiao'er Biantong granules Control: placebo Treatment duration: 2 weeks Rescue therapy: glycerine enema if no stool for 5 days (then considered noneffective)	Def: symptom score (consist of def frequency, consistency, straining, fecal incontinence) decrease of at least 90% compared to baseline. Time: 2 weeks	Reported	Def: number of children with ≥3 bowel movements per week Time: 2 weeks
Abdominal and acupressure point massage + traditional Chinese medicine vs traditional Chinese medicine					
Mao 2015	Age 4 – 13 years, N=94, Rome III	Intervention: addition of abdominal and acupressure point massage 25-30 min once a day Control: traditional Chinese medicine (Xingqi Daozhi Tongfu Fang) twice a day Treatment duration: 2 weeks Concurrent therapy both groups: toilet training,	Def: completely cured if decrease of severity score ≥95%, defecation frequency if 1/day or back to normal pattern, soft or mushy stools without straining.	NR	NR

		dietary advice to increase water, fiber, vegetable, and fruit intake, and advice to exercise more			
Xu 2015	Age 4 – 11 years, N=122, Rome III	Intervention: addition of abdominal and acupressure point massage daily 25-30 min Control: oral administration of traditional Chinese medicine twice daily Treatment duration: 2 weeks Concurrent therapy both groups: toilet training, dietary advice to eat light and easy digestible food, increase water, fiber, vegetable and fruit intake, and advice to exercise more.	Def: completely cured, decrease of symptom score ≥95% and bowel frequency once/day or back to normal pattern. Time: 2 weeks	NR	NR
Foot reflexology massage + toilet/diet/motivation training vs toilet/diet/motivation training					
Canbulat Sahiner 2017	Age 3 – 6 years, N=40, Rome III	Intervention: addition of 10 minute foot reflexology massage 5 days a week Control: toilet training, diet advice and motivation training with reward system 30 min once per week Treatment duration: 4 weeks	NR	Reported	Def: number of patients with more than 2 bowel movements per week Time: 4 weeks

		Concurrent therapy both groups: toilet training, dietary advice: lot of water and daily fruit and vegetables, honey with water every morning, legumes and max two slices whole wheat bread at least twice per day. Also, pasta, white rice, strawberries, banana, apple, potato, carrot, white bread, biscuits, and cake should not be eaten.			
Dry cupping vs laxatives					
Shahamat 2016	Age 4 – 18 years, N=120, Rome III	Intervention: cupping every other day 8 minutes (14 sessions of which 12 by parents) Control: PEG 0.4 g/kg Treatment duration: 4 weeks Concurrent therapy both groups: toilet training, routine nutritional and behavioral recommendations Rescue therapy: exclusion if no bowel movement for 7 days or fecal impaction at any stage.	Def: not fulfilling the Rome III criteria Time: 12 weeks	Reported	Def: number of patients with 2 or more bowel movements per week. Time: 12 week Data not adequately reported, unclear.

AE: adverse events, FC: functional constipation

Appendix 4. GRADE tabellen initiële medicamenteuze behandeling

1. Rectal enema vs oral medication

Notes: rectal enema: dioctylsulfosuccinate sodium, once daily for 6 days (60 ml children < 6 years, and 120 ml for children of 6 years and older). Maintenance therapy was started after 6 days of disimpaction: PEG3350 + electrolytes 0.5 g/kg/day for at least 2 weeks (follow-up period). Oral medication: PEG3350 + electrolytes 1.5 gr/kg per day for 6 days. Maintenance therapy was started after 6 days of disimpaction: PEG3350 + electrolytes 0.5 g/kg/day for at least 2 weeks (follow-up period).

Question: Should Rectal medication vs Oral medication be used for fecal impaction in functional constipation?

Bibliography: Bekkali 2009

GRADE

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal medication	Oral medication	Relative (95% CI)	Absolute		
Treatment success - absence of fecaloma on DRE. If children scared to undergo second DRE, X-ray performed (time of measurement: 6 days)												
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	37/46	30/44	RR: 1.18 (0.92 to 1.51)	123 more per 1000 (from 55 less to 348 more per 1000)	Very low	
Withdrawals due to adverse event (time of measurement: 3 weeks = 2 weeks after disimpaction)												
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	4/46	2/44	RR: 1.91 (0.37 to 9.92)	41 more per 1000 (from 29 less to 406 more per 1000)	Very low	
Defecation frequency per week - (time of measurement: 3 weeks = 2 weeks after disimpaction)												
1	randomised trials	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	N=41	N=39		MD: 1.00 lower (from 3.58 lower to 1.58 higher)	Low	
Stool consistency – number of patients with watery stools (time of measurement: 3 weeks = 2 weeks after disimpaction)												
1	randomised trials	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	4/41	13/39	RR: 0.29 (0.10 to 0.82)	237 less per 1000 (from 60 less to 300 less per 1000)	Low	
Fecal incontinence frequency per week - (time of measurement: 3 weeks = 2 weeks after disimpaction)[4]												
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]	Serious	N=41	N=39		MD: 0.80 lower (from 3.28 lower to 1.68 higher)	Very low	
Abdominal pain - assessed with: Bowel diary (time of measurement: 3 weeks = 2 weeks after disimpaction)												
1	randomised trials	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	23/41	17/39	RR 1.29 (0.82 to 2.01)	126 more per 1000 (from 78 less to 440 more)	Low	

[1] Downgraded one level because no safety data was reported

[2] Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to significant imprecision

[4]After 6 days mean (SD) fecal incontinence frequency per week was much higher in the PEG group: enema 3.4 (4.3) N=46, PEG: 13.6 (12.6) N=44 (MD: 10.20 lower (from 6.28 lower to 14.12 lower))

Appendix 5. GRADE tabellen onderhoudstherapie medicamenteuze behandeling

PEG

1. PEG vs placebo (N=3)

Question: Should Polyethylene glycol (PEG) vs placebo be used for functional constipation?

Bibliography: Modin 2018, Nurko 2008[1], Thomson 2007

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 2 weeks to 24 weeks)												
2	Randomised trials	Serious[2]	Not serious	Not serious	Serious[3]	Not serious	73/112	29/81	RR: 1.74 (1.25 – 2.41) NNT 4 (2-10)	265 more per 1000 (90 more to 505 more)	Moderate[4]	
Withdrawals due to Adverse Events at study end (range: 2 weeks to 24 weeks)												
2	Randomised trials	Serious[2]	Serious[5]	Not serious	Serious[3]	Not serious	4/112	3/81	RR: 0.92 (0.06 – 14.92)	3 less per 1000 (35 less to 515 more)	Very low	
Defecation frequency per week (time of measurement range: 2 weeks to 24 weeks)												
2	Randomised trials	Serious[2]	Serious[5]	Not serious	Serious[3]	Not serious	N=76	N=77		MD: 1.32 higher (0.15 lower to 2.79 higher)	Very low	
Stool consistency: reported on a scale from 0-4 (0 = too loose, watery to 4 = very hard) (time of measurement: 2 weeks)												
1	Randomised trials	Serious[2]	Not serious	Not serious	Serious[3]	Not serious	N = 53	N = 24		MD: 0.80 lower (from 1.38 lower to 0.22 lower)	Low	

Fecal incontinence frequency per week (time of measurement: 2 weeks)												
1	Randomised trials	Serious[2]	Not serious	Not serious	Very serious	Not serious	N = 53	N = 24		MD: 1.23 higher (from 0.52 lower to 2.98 more)	Very low	
Abdominal pain: cramping on a scale of 0-4 (0 = none to 4 = very painful) (time of measurement: 2 weeks)												
1	Randomised trials	Serious[2]	Not serious	Not serious	Serious[3]	Not serious	N = 53	N = 24		MD: 0.79 lower (from 1.35 lower to 0.23 lower)	Low	
Serious adverse events (time of measurement: 2 to 24 weeks)												
2	Randomised trials	Serious[2]	Not serious	Not serious	Very serious[6]	Not serious	0/111	1/81	RR: 0.15 (0.01 - 3.66)	10 less per 1000 (from 12 less to 33 higher per 1000)	Very low	
Adverse events (time of measurement: 2 weeks)												
1	Randomised trials	Serious[2]	Not serious	Not serious	Very serious	Not serious	33/53	14/24	RR: 1.07 (0.72 - 1.59)	41 more per 1000 (from 163 less to 344 more per 1000)	Very low	

[1]Nurko 2008 studied three groups with different dosages: 0.2, 0.4 and 0.8 g/kg. The group of 0.2 g/kg was left out of the analysis, because this dosage is not used in clinical practice and would affect the results. Groups 0.4 and 0.8 g/kg were combined in analysis.

[2]Downgraded one level due to unclear allocation concealment and reporting

[3]Downgraded one level due to imprecision.

[4]Risk of bias and imprecision were both dubious, therefore the overall quality was assessed as moderate instead of low.

[5]Downgraded one level due to serious inconsistency

[6]Downgraded two levels due to very limited number of events

2. PEG vs Lactulose (N=8)

Notes: Dupont 2005 only included children aged 6 months – 3 years old. Treepongkaruna 2014 only included children aged 12 – 36 months old.
Question: Should Polyethylene glycol (PEG) vs lactulose be used for functional constipation?
Bibliography: Dheivamani 2021, Dupont 2005, Jarzebicka 2019, Saneian 2012, Treepongkaruna 2014, Uhm 2007, Voskuijl 2004, Wang 2007

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyethylene glycol	Lactulose	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 2 weeks to 12 months)												
5	randomised trials	Serious[1]	Serious	Not serious	Serious[2]	Not serious	207/288	151/297	RR 1.35 (1.11 to 1.64) NNT: 5 (range 3 – 16)	201 more per 1000 (from 63 more to 368 more)	Low	
Withdrawals due to Adverse Events at study end (range 2 weeks to 12 months)												
6	randomised trials	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	19/272	20/272	RR 0.97 (0.47 to 2.00)	4 less per 1000 (from 38 less to 74 more)	Low	
Defecation frequency per week (time of measurement range: 4 weeks to 3 months)												
6[3]	randomised trials	Serious[1]	Very serious[4]	Not serious	Serious[5]	Not serious	N = 254	N = 246		SMD 1.10 (0.13 to 2.07)	Very low[6]	
Painful defecation: number of patients with painful defecation												
3	randomised trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	24/151	47/151	RR: 0.54 (0.27 to 1.07)	143 less per 1000 (from 227 less to 22 more per 1000)	Very low	
Stool consistency: compared to baseline 0 = harder stool, 1 = no change from baseline, 2 = softer stool. Number of patients with improved stool consistency (time of measurement: 4 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious	Not serious	24/43	27/44	RR: 0.80 (0.34 to 1.87)	123 less per 1000 (from 405 less to 534 more per 1000)	Low	

Fecal incontinence frequency per week (time of measurement: 8 weeks)											
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	N = 46	N = 45		MD: 0.27 higher (1.61 lower to 2.15 higher)	Very Low	
Abdominal pain – number of patients with abdominal pain (time of measurement: 8 weeks)											
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	16/50	25/50	RR: 0.64 (0.39 to 1.04)	180 less per 1000 (from 305 less to 20 more per 1000)	Very low	
Serious adverse events											
6	Randomised trials	Serious[1]	Not serious	Not serious	Very serious[7]	Not serious	2/328	1/334	RR: 2.00 (0.19 - 21.26)	3 more per 1000 (from 2 less to 61 more per 1000)	Very low	
Adverse events											
5	Randomised trials	Serious[1]	Not serious	Not serious	Serious	Not serious	59/215	72/220	RR: 0.85 (0.69 to 1.06)	49 less per 1000 (from 101 less to 20 more per 1000)	Low	

[1]Downgraded one level due to lack of blinding in all studies

[2]Downgraded one level due to significant imprecision. Range in treatment success is very wide and NNT = 7.

[3]Dupont: defecation frequency reported as median (IQR), converted to mean (SD)

[4]Downgraded two levels due to significant inconsistency (I^2 = 96%). Jarzebicka 2019 causes a high I^2 of 96%. No clinical explanation was found for the high heterogeneity. Therefore, sensitivity analysis was performed, leaving Jarzebicka 2019 out of the meta-analysis. This resulted in a heterogeneity of I^2=0% and inconsistency would be graded as 'not serious'. Without Jarzebicka, imprecision would also be graded as 'not serious', leading to an overall quality assessment of 'moderate' instead of 'very low'.

[5]Downgraded one level due to significant imprecision

[6]Sensitivity analysis of Jarzebicka would lead to an overall quality assessment of 'moderate'

[7]Downgraded two levels due to limited number of events

3. PEG vs Magnesium hydroxide (N=4)

Question: Should Polyethylene glycol (PEG) vs magnesium hydroxide be used for functional constipation?

Bibliography: Gomes 2011, Loening-Baucke 2006, Ratanamongkol 2009, Saneian 2012

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyethylene glycol	MgOH	Relative (95% CI)	Absolute		
Treatment success (measured at 4 weeks)												
1	randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	42/47	28/47	RR: 1.50 (1.16 to 1.94) NNT: 3 (rang 2 – 10)	290 more per 1000 (from 96 more to 564 more)	Very low	
Withdrawals due to Adverse Events at study end (range: 4 weeks to 12 moths)												
3	randomised trials	Serious[3]	Not serious	Not serious	Serious[2]	Not serious	6/103	18/108	RR: 0.38 (0.16 to 0.92)	104 less per 1000 (from 140 less to 13 less)	Low	
Defecation frequency per week (time of measurement range: 4 weeks to 3 months)												
4	randomised trials	Very serious[4]	Very serious[5]	Not serious	Not serious	Not serious	N = 127	N = 115		MD -0.02 (-1.20 – 1.16)	Very low	
Painful defecation: number of patients with episodes of painful defecations.												
1	randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	2/47	11/47	RR: 0.18 (0.04 to 0.78)	192 less per 1000 (from 225 less to 51 less per 1000)	Very low	
Serious adverse events												

2	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[6]	Not serious	0/85	0/83	Not estimable	Not estimable	Very low	
Adverse events												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	20/46	24/43	RR: 0.78 (0.51 - 1.19)	123 less per 1000 (from 273 less to 106 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding and unclear selective reporting bias
[2]Downgraded one level due to significant imprecision from sparse data
[3]Downgraded one level due to lack of blinding
[4]Downgraded two levels due to lack of blinding and selective reporting bias/attrition bias
[5]Downgraded two levels due to substantial heterogeneity
[6]Downgraded two levels due to no events

4. PEG vs Sodiumpicosulfate (N=1)

Question: Should PEG vs sodiumpicosulfate be used for treatment of functional constipation in children?
Bibliography: Cassetari 2019

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEG**	**Sodiumpicosulfate**	**Relative (95% CI)**	**Absolute**		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency – Dichotomous: number of patients having more than 3 bowel motions per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		10/16	8/17	RR: 1.33 (0.71 – 2.50)	155 per 1000 more (136 fewer to 709 more)	Low	

Painful defecation (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		4/16	2/17	RR: 2.13 (0.45 - 10.05)	133 more per 1000 (from 65 fewer to 1000 more per 1000)	Low	
Stool consistency (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		11/16	13/17	RR: 0.90 (0.59 - 1.37)	76 fewer per 1000 (from 336 fewer to 283 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		4/16	5/17	RR: 0.85 (0.28 - 2.61)	26 fewer per 1000 (from 127 fewer to 284 more per 1000)	Low	
Abdominal pain (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		2/16	5/17	RR: 0.42 (0.10 - 1.89)	171 fewer per 1000 (from 265 fewer to 262 more per 1000)	Low	
Adverse events												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		0/16	0/17	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

5. PEG vs Sodium picosulfate + fibers (N=1)

Notes: Cassettari 2019 compared PEG with sodium picosulfate and green banana biomass. Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.

Question: Should PEG vs sodium picosulfate in combination with fibers be used for treatment of functional constipation?

Bibliography: Cassettari 2019

GRADE

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Sodium picosulfate + fibers	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency – dichotomous: number of patients having more than 3 bowel motions per week												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	10/16	15/16	RR: 0.67 (0.45 – 0.99)	31 fewer per 1000 (9 fewer to 515 fewer)	Low	
Painful defecation (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	4/16	1/16	RR: 4.00 (0.50 - 31.98)	188 more per 1000 (from 31 fewer to 1000 more per 1000)	Low	
Stool consistency - Number of patients with Bristol Stool Form Scale higher than 1 or 2 (hard stools) (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	11/16	13/16	RR: 0.85 (0.56 - 1.27)	122 fewer per 1000 (from 358 fewer to 219 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	4/16	2/16	RR: 2.00 (0.42 - 9.42)	125 more per 1000 (from 73 fewer to 1000 more per 1000)	Low	
Abdominal pain (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/16	4/16	RR: 0.50 (0.11 - 2.35)	125 fewer per 1000 (from 223 fewer to 338 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		0/16	0/17	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

6. PEG vs Liquid paraffin (N=2)

Question: Should PEG vs liquid paraffin be used for functional constipation?

Bibliography: Karami 2009, Rafati 2011

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Liquid paraffin	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events at study end (4 months)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	0/80	2/80	RR: 0.20 (0.01 – 4.1)	20 less per 1000 (from 25 less to 78 more)	Very low	
Defecation frequency per week (time of measurement range: 1 to 4 months)												
2	Randomised trials	Very serious[1]	Serious[3]	Not serious	Serious[2]	Not serious	N = 128	N = 133		MD: 0.65 higher (from 0.33 lower to 1.62 higher)	Very low	
Fecal incontinence frequency per month (time of measurement: 4 weeks)												
1	Randomised trails	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 48	N = 55		MD: 0.00 (from 0.12 lower to 0.12 higher)	Low	
Fecal incontinence: number of patients with fecal incontinence (time of measurement: 4 weeks)												
1	Randomised trails	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	12/80	10/78	RR: 1.17 (0.54 - 2.55)	23 more per 1000 (from 59 less to 199 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding and high risk of attrition bias and selective reporting
[2]Downgraded one level due to significant imprecision from extremely sparse data
[3]Downgraded one level due to considerable heterogeneity

7. PEG vs enema (N=1)

Notes: Included children aged 6 months to 4 years. The study investigated Promelaxin microenema (4 ml/5g).
Question: Should PEG vs enemas be used for the treatment of functional constipation?
Bibliography: Strisciuglio 2021

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Enema	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 2 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	43/77	55/76	RR: 0.77 (0.61 – 0.98) NNT: -6 (-70 to -4)	167 fewer per 1000 (282 fewer to 15 fewer)	Very low	
Withdrawals due to Adverse Events (time of measurement: 8 weeks)												
1	Randomised trials	Very serious	Not serious	Not serious	Serious[2]	Not serious	17/77	24/76	RR: 0.70 (0.41 – 1.19)	95 fewer per 1000 (186 fewer to 60 more)	Very low	
Defecation frequency – not reported												
Stool consistency: number of patients with improved stool consistency (time of measurement: 8 weeks)												
1	Randomised trials	Very serious	Not serious	Not serious	Serious[2]	Not serious	37/77	38/76	RR: 0.96 (0.70 – 1.33)	20 less per 1000 (from 150 less to 165 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding and due to the fact that after the initial 14 days of treatment, the participants received self-directed variable amounts of the agent, which could have affected the composition of the treatment groups.
[2]Downgraded one level due to significant imprecision

8. PEG4000 vs PEG3350 + Electrolytes (N=2)

Question: Should PEG4000 vs PEG3350 + electrolytes be used for treatment of functional constipation?

Bibliography: Bekkali 2018, Savino 2012

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG4000	PEG3350 + Electrolytes	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 52 weeks)												
1	randomised trials	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	22/49	24/48	RR: 0.90 (0.59 – 1.37)	50 less per 1000 (205 less to 185 more)	Low	
Withdrawals due to Adverse Events (time of measurement range: 4 to 52 weeks)												
2	randomised trials	Serious[3]	Not serious	Not serious	Very serious[4]	Not serious	4/99	10/94	RR 0.42 (0.15 – 1.19)	61 less per 1000 (90 less to 20 more)	Very low	
Defecation frequency per week (time of measurement range: 4 to 52 weeks)												
2	randomised trials	Serious[3]	Very serious	Not serious	Very serious[4]	Not serious	N = 94	N = 81		MD: 0.15 lower (from 3.37 lower to 3.08 higher)	Very low	
Serious adverse events (time of measurement: 52 weeks)												
1	Randomised trials	Serious[1]	Not serious	Not serious	Very serious[4]	Not serious	0/49	2/48	RR: 0.20 (0.01 to 3.98)	33 less per 1000 (from 41 less to 124 more per 1000)	Very low	
Adverse events (time of measurement: 52 weeks)												

1	Randomised trials	Serious[1]	Not seriosu	Not serious	Very serious	Not serious	28/49	28/48	RR: 0.98 (0.70 - 1.38)	12 less per 1000 (from 175 less to 222 more per 100)	Very low	

[1]Downgraded one level due to high risk of attrition bias
[2]Downgraded one level due to significant imprecision
[3]Downgraded one level due to lack of blinding and high risk of attrition bias
[4]Downgraded two levels due to very serious imprecision

9. PEG vs fibers (N=2)

Notes:

Cassetari 2019 investigates green banana biomass: Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.

Quitadamo 2012 investigates the mixture of acacia fiber, psyllium fiber (67.7% and 17.3%, respectively), and fructose (AFPFF): "*a supplement designed to enrich dietary fiber. The characteristics of low interference with the absorption of water and nutrients, together with the acacia and psyllium fiber's low swelling index, make it a compound fit for use in the treatment of CFC."*

Question: Should Polyethylene glycol (PEG) vs fibers be used for functional constipation?

Bibliography: Cassettari 2019, Quitadamo 2012

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Polyethylene glycol**	**Fibers**	**Relative (95% CI)**	**Absolute**		
Treatment success (measured at 8 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	39/50	28/50	RR: 1.39 (1.05 – 1.85) NNT: 6 (2 – 36)	218 more per 1000 (28 more to 476 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 8 weeks)												

1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	1/50	0/50	RR: 3.00 (0.13 to 71.92)	40 more per 1000 (from 17 less to 1000 more per 1000)[6]	Very low	
Defecation frequency per week (time of measurement: 8 weeks)[4]												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=47	N=36		MD: 0.20 stools per week more (0.64 stools per week less to 1.04 stools per week more)	Low	
Defecation frequency - number of patients with more than 3 bowel movements per week (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	10/16	9/15	RR: 1.04 (0.59 to 1.83)	24 more per 1000 (from 246 less to 500 more per 1000)	Low	
Painful defecation – number of patients with painful stools (time of measurement: 8 weeks)												
2	Randomised trials	Serious	Not serious	Not serious	Serious	Not serious	8/66	11/65	RR: 0.73 (0.32 to 1.67)	46 less per 1000 (from 115 less to 113 more per 1000)	Low	
Serious adverse events (time of measurement: 8 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[5]	Not serious	0/50	0/50	Not estimable	Not estimable	Very low	
Adverse events (time of measurement: 8 weeks)												
2	Randomised trials	serious	Not serious	Not serious	Very serious[5]	Not serious	0/66	0/65	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding and unclear allocation concealment and selective reporting
[2]Downgraded two levels due to significant imprecision from sparse data
[3]Downgraded two levels due to significant imprecision from sparse data
[5]Downgraded two levels due to no events
[6]Added one fictional case to the control group in RevMan to calculate absolute numbers in order to better interpret results

10. PEG + fibers vs fibers (N=1)

Notes: Cassettari 2019 compared PEG with green banana biomass. Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.
Question: Should Polyethylene glycol (PEG) as addition to fibers vs fibers alone be used for functional constipation?
Bibliography: Cassettari 2019

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG + fibers	Fibers	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency – Dichotomous: number of patients having more than 3 bowel motions per week (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	12/16	9/15	RR: 1.25 (0.76 – 2.06)	150 more per 1000 (from 144 less to 637 more)	Low	
Painful defecation (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	3/16	4/15	RR: 0.70 (0.19 - 2.63)	80 fewer per 1000 (from 216 less to 435 more per 1000)	Low	
Stool consistency (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	15/16	13/15	RR: 1.08 (0.85 - 1.37)	69 more per 1000 (from 130 less to 321 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/16	5/15	RR: 0.38 (0.09 - 1.65)	207 fewer per 1000 (from 303 less to 217 more per 1000)	Low	

Abdominal pain (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/16	2/15	RR: 0.94 (0.15 - 5.84)	8 fewer per 1000 (from 113 less to 645 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	0/16	0/17	Not estimable	Not estimable	Very low[2]	

[1]Downgraded two levels due to significant imprecision from extremely sparse data

[2]Graded as very low due to such sparse data and lack of events assessments for serious events are of very low certainty

11. PEG vs prebiotic (N=1)

Notes: prebiotics included Pysllium Seed Husk Powder

Question: Should PEG vs prebiotics be used for the treatment of functional constipation?

Bibliography: Foroughi 2022[1]

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Prebiotic	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency per week (time of measurement: 3 weeks)												
1	randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 36	N = 36		MD: 1.41 higher (1.20 higher to 1.62 higher)	Low	
Number of painless bowel movements per week (time of measurement: 3 weeks)												
1	randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 36	N = 36		MD: 1.58 higher (0.98 higher to 2.18 higher)	Low	

[1]Downgraded two levels due to unclear method of randomization and allocation and unclear attrition and selective reporting

12. PEG vs prebiotic + probiotics (N=1)

Notes: prebiotics included Pysllium Seed Husk Powder. Probiotics consisted of a mixture of Lactobacillus reuteri, Lactobacillus rhamnosus, and Bifidobacterium infantis.

Question: Should PEG alone vs prebiotics with the addition of probiotics be used for the treatment of functional constipation?

Bibliography: Foroughi 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Prebiotic + probiotics	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency per week (time of measurement: 3 weeks)												
1	randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 36	N = 36		MD: 0.75 higher (0.36 higher to 1.14 higher)	Low	
Number of painless bowel movements per week (time of measurement: 3 weeks)												
1	randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	N = 36	N = 36		MD: 0.89 higher (0.35 higher to 1.43 higher)	Very low	

[1]Downgraded two levels due to unclear method of randomization and allocation and unclear attrition and selective reporting

13. PEG + probiotics vs prebiotic (N=1)

Notes: prebiotics included Pysllium Seed Husk Powder. Probiotics consisted of a mixture of Lactobacillus reuteri, Lactobacillus rhamnosus, and Bifidobacterium infantis.

Question: Should PEG with the addition of probiotics vs prebiotics alone be used for the treatment of functional constipation?

Bibliography: Foroughi 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG + probiotics	Prebiotic	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency												
1	randomised trials	Very serious[2]	Not serious	Not serious	Not serious	Not serious	N = 36	N = 36		MD: 1.55 higher (1.37 higher to 1.73 higher)	Low	
Number of painless bowel movements per week (time of measurement: 3 weeks)												
1	randomised trials	Very serious[2]	Not serious	Not serious	Not serious	Not serious	N = 36	N = 36		MD: 1.86 higher (1.33 higher to 2.39 higher)	Low	

[1]Foroughi 2022 compared PEG + probiotics vs Pysllium Seed Husk Powder (prebiotic). Probiotics consisted of a mixture of Lactobacillus reuteri, Lactobacillus rhamnosus, and Bifidobacterium infantis.

[2]Downgraded two levels due to unclear method of randomization and allocation and unclear attrition and selective reporting

14. PEG vs herbal medicine (N=7)

Question: Should Polyethylene glycol (PEG) vs herbal medicine be used for functional constipation?

Bibliography: Dehghani 2019, Esmaeilidooki 2016, Imanieh 2022, Nasri 2022, Nimrouzi 2015, Saneian 2021, Tavassoli 2021

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyethylene glycol	Herbal medicine	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 4 to 8 weeks)												
4	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	115/164	116/157	RR: 0.98 (0.86 to 1.12)	15 less per 1000 (from 108 less to 93 more per 1000)	Very low	
Withdrawals due to Adverse Events (time of measurement range: 4 to 8 weeks)												
7	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	12/374	8/367	RR: 1.44 (0.60 – 3.45)	10 more per 1000 (from 9 less to 53 more per 1000)	Very low	
Defecation frequency per week (time of measurement range: 3 to 8 weeks)												
4	Randomised trials	Very serious[1]	Serious[3]	Not serious	Serious[2]	Not serious	N = 203	N = 205		MD: 1.22 lower (from 2.79 lower to 0.34 higher)	Very low	
Painful defecation: number of patients with painful defecations (time of measurement: 8 weeks)												
2	Randomised trials	Very serious[4]	Not serious	Not serious	Serious[2]	Not serious	25/90	28/90	RR: 0.90 (0.57 to 1.42)	31 less per 1000 (from 134 less to 131 more per 1000)	Very low	
Stool consistency: frequency of hard stools per week (time of measurement: 3 to 4 weeks)												

2	Randomised trials	Very serious[4]	Serious	Not serious	Serious	Not serious	N = 119	N = 123		MD: 0.45 more number of hard stools per week (from 0.49 less to 1.39 more hard stools per week)	Very low	
Fecal incontinence: frequency of fecal incontinence per week (time of measurement: 3 to 4 weeks)												
3	Randomised trials	Very serious[4]	Not serious	Not serious	Serious	Not serious	N = 176	N = 175		MD: 0.21 episode of fecal incontinence per week more (from 0.44 episode less to 0.87 episode of fecal incontinence more per week)	Very low	
Adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[2]	Not serious	7/47	4/45	RR: 1.68 (0.53 - 5.34)	60 more per 1000 (from 42 less to 386 more per 1000)	Low	

[1]Downgraded two levels for lack of blinding and unclear allocation bias

[2]Downgraded one level for significant imprecision

[3]Downgraded one level due to substantial heterogeneity

[4]Downgraded two levels for lack of blinding, unclear allocation bias and selective reporting

15. PEG vs dry cupping (N=1)

Question: Should PEG vs dry cupping be used for treatment of functional constipation?

Bibliography: Shahamat 2016

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG	Dry cupping	Relative (95% CI)	Absolute		
Treatment success: not fulfilling the Rome III criteria (time of measurement: 12 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	50/60	46/60	RR: 1.09 (0.91 - 1.30)	69 more per 1000 (from 69 less to 230 more per 1000)	Very low	
Withdrawals due to adverse events (time of measurement: 12 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	0/60	2/60	RR: 0.20 (0.01 - 4.08)	27 less per 1000 (from 33 less per to 103 more per 1000)	Very low	
Defecation frequency: number of patients with 2 or more bowel movements per week (time of measurement: 12 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	52/60	53/60	RR: 0.98 (0.86 - 1.12)	18 less per 1000 (from 124 less to 106 more per 1000)	Very low	
Fecal incontinence: number of patients with 1 ≤ episode of fecal incontinence/week (time of measurement: 12 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	50/60	55/60	RR: 0.91 (0.79 - 1.04)	83 less per 1000 (from 193 less to 37 more per 1000)	Very low	

[1]Downdgraded two levels due to lack of blinding and unclear allocation concealment and reporting

[2]Downgraded one level due to significant imprecision

16. PEG vs manual therapy (N=1)

Question: Should PEG vs manual therapy be used for treatment of functional constipation?

Bibliography: Blanco Diaz 2020

GRADE

See GRADE tables of non-pharmacological treatment

Lactulose

1. Lactulose vs placebo (N=1)

Question: Should lactulose vs placebo be used for treatment of functional constipation?

Bibliography: Cao 2018

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactulose	placebo	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events at study end (time of measurement: 6 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]		4/50	5/50	RR: 0.8 (0.23 – 2.81)	20 fewer per 1000 (77 fewer to 181 more)	Low	
Defecation frequency – not adequately reported[2]												
Serious adverse events (time of measurement: 6 weeks)												

1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]		0/50	0/50	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

2. Lactulose vs lactitol (N=1)

Question: Should lactulose vs lactitol be used as treatment of functional constipation?

Bibliography: Pitzalis 1995[1]

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lactulose**	**lactitol**	**Relative (95% CI)**	**Absolute**		
Treatment success - not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[2]	Not serious	Not serious	Serious[3]		N = 19	N = 23		MD: 0.80 lower (2.55 lower to 0.95 more)	Very low	
Painful defecation (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[2]	Not serious	Not serious	Very serious[4]		8/24	6/27	RR: 1.50 (0.61 to 3.71)	111 more per 1000 (from 87 less to 602 more per 1000)	Very low	
Fecal incontinence (time of measurement: 4 weeks)												

1	Randomised trials	Very serious[2]	Not serious	Not serious	Very serious[4]		15/24	12/27	RR: 1.41 (0.83, 2.37)	182 more per 1000 (76 less to 609 more per 1000)	Very low	
Abdominal pain (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[2]	Not serious	Not serious	Very serious[4]		15/24	9/27	RR: 1.88 (1.01, 3.47)	293 more per 1000 (from 3 more to 892 more per 1000)	Very low	

[1]Study was translated from Italian

[2]Downgraded two levels due to lack of blinding and unclear method of randomization, allocation and incomplete reporting of dropouts

[3]Downgraded one level due to significant imprecision

[4]Downgraded two levels due to very serious imprecision

3. Lactulose vs Magnesium hydroxide (N=1)

Question: Should lactulose vs magnesium hydroxide be used as treatment of functional constipation?

Bibliography: Saneian 2012

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lactulose**	**Magnesium hydroxde**	**Relative (95% CI)**	**Absolute**		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]		N = 30	N = 30		MD: 1.51 lower (2.53 lower to 0.49 lower)	Very low	

[1]Downgraded two levels due to lack of blinding and high risk of selective reporting

[2]Downgraded one level due to significant imprecision

4. Lactulose vs liquid paraffin (N=2)

Question: Should lactulose vs liquid paraffin be used for functional constipation?

Bibliography: Farahmand 2007, Urganci 2005

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactulose	Liquid paraffin	Relative (95% CI)	Absolute		
Treatment success (time of measurement: week 4-8)												
2	Randomised trials	Very serious[1]	Very serious	Not serious	Serious[2]	Not serious	51/140	128/147	RR: 0.53 (0.18 – 1.51)	410 less per 1000 (714 less to 444 more)	Very low	
Withdrawals due to Adverse Events (time of measurement: 8 weeks)												
2	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	17/140	20/147	RR: 0.90 (0.50-1.63)	14 less per 1000 (68 less to 86 more)	Very low	
Defecation frequency per week (time of measurement: week 4-8)												
2	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 140	N = 147		MD: 4.94 lower (5.61 lower to 4.28 lower)[5]	Low	
Stool consistency: based on a scale of 1-3 (1=hard, 2=firm, 3=loose stools) (time of measurement: week 4-8)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=20	N=20		MD: 0.09 lower (0.29 lower to 0.11 higher)	Low	
Fecal incontinence frequency (time of measurement: week 4-8)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=120	N=127		Not estimable[6]	Very low	
Serious adverse events (time of measurement: 8 weeks)												

1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[4]	Not serious	0/120	0/127	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to unclear randomization and allocation and lack of blinding
[2]Downgraded one level due to significant imprecision
[3]Downgraded two levels due to serious imprecision
[4]Downgraded two levels due to no events in both groups
[5]Relatively high numbers: mean age of children was approximately 4 years in both studies. With max age 7 years
[6]Mean (SD): liquid paraffin: 0 (0), Lactulose: 3 (4.1)

5. Lactulose + PEG vs PEG (N=1)

Notes: Initial randomized treatment period was 4 weeks, after these 4 weeks patients who were successfully treated were followed for 12 months in order to investigate recurrence rates.
Question: Should lactulose as addition to PEG vs PEG alone be used for the treatment of functional constipation?
Bibliography: Ala 2015

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEG + Lactulose**	**PEG**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	87/100	70/100	RR: 1.24 (1.07 – 1.44) NNT: 6 (3 to 20)	168 more per 1000 (50 more to 308 more)	Very low	
Withdrawals due to Adverse Events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	7/100	0/100	RR: 15.00 (0.87 – 259.16)	140 more per 1000 (from 1 less to 1000 more per 1000)	Very low	
Defecation frequency – not reported												

Adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	15/100	0/100	RR: 31.00 (1.88 - 511.12)	300 more per 1000 (from 9 more to 1000 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding and unclear allocation concealment, attrition bias and selective reporting
[2]Downgraded one level due to significant imprecision
[3]Downgraded two levels due to very sparse data and significant imprecision

6. Lactulose vs fibers (N=2)

Notes: In Kokke 2008 both groups received a yoghurt drink containing either a fiber mixture or lactulose. The fiber mixture consisted of transgalacto-oligosaccharides, inulin, soy fiber, and resistant starch. Üstündağ 2010 investigated partially hydrolyzed guar gum (PHGG), which is a fiber source with low viscosity and it is completely fermented in the colon.
Question: Should lactulose vs fibers be used for treatment of functional constipation?
Bibliography: Kokke 2008, Usdundag 2010

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactulose	Fibers	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events (time of measurement: 4 weeks to 12 weeks)												
2	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	5/103	5/100	RR: 0.99 (0.29 – 3.36)	1 less per 1000 (from 36 less to 118 more)	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												

1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 30	N = 31		MD: 1.00 higher (from 0.28 higher to 1.72 higher)	Very low	
Stool consistency: Bristol Stool Form Scale (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 30	N = 31		MD: 0.40 higher (from 1.41 lower to 2.21 higher)	Very low	
Fecal incontinence- number of patients with 1 or more fecal incontinence epidsodes per week. (time of measurement: 4 weeks)												
1	Randomised trials	very serious	Not serious	Not serious	Serious[2]	Not serious	5/70	9/65	RR: 0.52 (0.18 - 1.46)	66 less per 1000 (from 114 less to 64 more per 1000)	Very low	
Abdominal pain (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	3/33	5/35	RR: 0.64 (0.16 - 2.45)	51 less per 1000 (from 120 less to 207 more per 1000)	Very low	
Serious adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	0/70	0/65	Not estimable	Not estimable	Very low	
Adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	2/70	1/65	RR: 1.86 (0.17 - 20.00)	13 more per 1000 (from 13 less to 292 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding, high risk of selective reporting and unclear allocation concealment

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to very sparse data

7. Lactulose vs probiotic (N=2)

Notes: Lee 2022 investigated probiotic S. boulardii and Olgaç 2013 investigated L. reuteri.

Question: Should lactulose vs probiotics be used for the treatment of functional constipation?

Bibliography: Lee 2022, Olgaç 2013

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactulose	Probiotics	Relative (95% CI)	Absolute		
Treatment success (time of measurement: at 12 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	18/69	4/50	RR: 3.26 (1.18 – 9.05) NNT: 6 (2 to 69)	181 more per 1000 (from 14 more to 644 more per 1000)	Very low	
Withdrawals due to Adverse Events (time of measurement: 2-12 weeks)												
2	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	53/97	50/75	RR: 0.76 (0.64 – 0.92)	160 less per 1000 (from 53 less to 240 less per 1000)	Very low	
Defecation frequency per week (time of measurement: range 2 to 4 weeks)												
2	Randomised trials	Very serious[1]	Serious[3]	Not serious	Not serious	Not serious	N=88	N=64		MD: 0.20 stools less per week (from 0.86 stools less per week to 0.46 stools more per week)	Very low	
Painful defecation (time of measurement: 2 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=60	N=37		MD: 0.20 painful stools less per week (from 0.47 painful stools less per week to 0.07 painful stools more per week)	low	
Stool consistency Bristol Stool Form Scale (time of measurement: range 2 – 4 weeks)												
1	Randomised trials	Very serious[1]	Serious	Not serious	Not serious	Not serious	N=88	N=62		MD: 0.17 higher score on BSFS (from 0.26 lower score to 0.61 higher score on BSFS scale)	Very low	

Fecal incontinence frequency per week (time of measurement: 2 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[3]	Not serious	N=60	N=37		MD: 0.43 number of times less fecal incontinence per week (from 1.68 number of times less incontinence to 0.82 number of times more incontinence per week)	Very low	

[1]Downgraded two levels due to lack of blinding and incomplete outcome data

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to significant heterogeneity

[4]Downgraded one level due to significant imprecision

Magnesium oxide

1. Magnesium oxide vs probiotics (N=1)

Question: Should magnesium oxide vs probiotics be used as treatment for functional constipation?

Bibliography: Bu 2007, Kubota 2020[4]

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Magnesium oxide	Probiotics	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	13/18	14/18	RR: 0.93 (0.64 - 1.36)	54 less per 1000 (from 280 less to 280 more per 1000)	Very low	
Withdrawals due to adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/18	1/18	RR: 2.00 (0.20 - 20.15)	56 more per 1000 (from 44 less to 1000 more per 1000)	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[3]	Not serious	N = 18	N = 18		MD: 0.28 lower (1.14 lower to 0.58 higher)	Very low	
Stool consistency: Percentage of hard stools (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[3]	Not serious	N = 18	N = 18		MD: 1.10 (from 6.61 lower to 8.81 higher)	Very low	
Fecal incontinence – unclear if frequency is per week or per month, therefore not reported												
1												
Abdominal pain frequency – unclear if frequency is per week or per month, therefore not reported												

1												
Adverse events												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	1/18	0/18	RR: 3.17 (0.12 - 83.17)	Not estimable	Very low	

[1]Downdgraded two levels due to unclear method of allocation, attrition and reporting

[2]Downgraded two levels due to significant imprecision and sparse data

[3]Downgraded one level due to significant imprecision

[4]Kubota 2020 reports change from baseline as least square means, therefore not added to the meta-analyses.

2. Magnesium oxide + probiotics vs probiotics (N=1)

Question: Should magnesium oxide as addition to probiotics vs probiotics alone be used for treatment of functional constipation?
Bibliography: Kubota 2020

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Magnesium oxide + probiotics**	**Probiotics**	**Relative (95% CI)**	**Absolute**		
Treatment success – not reported												
Withdrawals due to adverse events (time of measurement: 4 weeks) – not reported per group												
1												
Defecation frequency per week (time of measurement: 4 weeks) – reported as change from baseline in least square means												
1												
Stool consistency (time of measurement: 4 weeks) – Bristol stool form scale, reported as change from baseline in least square means.												

1												

3. Magnesium oxide vs placebo (N=1)

Question: Should magnesium oxide vs placebo be used for treatment of functional constipation?

Bibliography: Bu 2007

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Magnesium oxide	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	13/18	1/9	RR: 6.50 (1.00 - 42.17)	611 more per 1000 (from 0 more to 1000 more per 1000)	Very low	
Withdrawals due to adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/18	1/9	RR: 1.00 (0.10 - 9.61)	0 more per 1000 (from 100 less to 957 more per 1000)	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 18	N = 9		MD: 2.15 higher (from 1.46 higher to 2.84 higher)	Low	
Stool consistency: Percentage of hard stools (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N = 18	N = 9		MD: 52.00 lower (57.40 lower to 46.60 lower)	Low	
Fecal incontinence – unclear if frequency is per week or per month, therefore not reported												
1												

Abdominal pain frequency – unclear if frequency is per week or per month, therefore not reported												
1												
Adverse events												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	1/18	0/9	RR: 3.17 (0.12 - 83.17)	Not estimable	Very low	

[1]Downdgraded one level due to unclear allocation concealment, attrition and selective reporting

[2]Downgraded two levels due to significant imprecision and sparse data

Sodium picosulfate

1. Sodium picosulfate vs PEG + fibers (N=1)

Notes: Cassettari 2019 compared sodium picosulfate with PEG and green banana biomass. Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.

Question: Should sodium picosulfate vs PEG in combination with fibers be used for treatment of functional constipation?

Bibliography: Cassettari 2019

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium picosulfate**	**PEG + fibers**	**Relative (95% CI)**	**Absolute**		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency – Dichotomous: number of patients having more than 3 bowel motions per week												

1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	8/17	12/16	RR: 0.63 (0.35 – 1.12)	278 fewer per 1000 (from 488 fewer to 90 more)	Low	
Painful defecation (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/17	3/16	RR: 0.63 (0.12 - 3.28)	69 fewer per 1000 (from 165 fewer to 428 more per 1000)	Low	
Stool consistency - number of patients with Bristol Stool Form Scale higher than 1 or 2 (hard stools) (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	13/17	15/16	RR: 0.82 (0.61 - 1.09)	169 fewer per 1000 (from 366 fewer to 84 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	5/17	2/16	RR: 2.35 (0.53 - 10.45)	169 more per 1000 (from 59 fewer to 1000 more per 1000)	Low	
Abdominal pain (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	5/17	2/16	RR: 2.35 (0.53 - 10.45)	169 more per 1000 (from 59 fewer to 1000 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		0/16	0/17	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

2. Sodium picosulfate vs fibers (N=1)

Notes: Cassettari 2019 compared sodium picosulfate with green banana biomass. Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.

Question: Should sodium picosulfate vs fibers be used for treatment of functional constipation?

Bibliography: Cassettari 2019

GRADE

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium picosulfate	Fibers	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency – Dichotomous: number of patients having more than 3 bowel motions per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	8/17	9/15	RR: 0.78 (0.41 – 1.51)	132 fewer per 1000 (from 355 fewer to 306 more)	Low	
Painful defecation (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/17	4/15	RR: 0.44 (0.09 - 2.08)	149 fewer per 1000 (from 242 fewer to 288 more per 1000)	Low	
Stool consistency - Number of patients with Bristol Stool Form Scale higher than 1 or 2 (hard stools) (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	13/17	13/15	RR: 0.88 (0.63 - 1.23)	104 fewer per 1000 (from 321 fewer to 199 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	5/17	5/15	RR: 0.88 (0.32 - 2.46)	40 fewer per 1000 (from 227 fewer to 487 more per 1000)	Low	
Abdominal pain (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	5/17	2/15	RR: 2.71 (0.44 - 16.68)	228 more per 1000 (from 75 fewer to 1000 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]		0/16	0/17	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

3. Sodium picosulfate + fibers vs fibers (N=1)

Notes: Cassettari 2019 compared sodium picosulfate with green banana biomass. Green (unripe) banana contains a high amount of fiber and a high concentration of amylase-resistant starch, which is not digested or absorbed in the intestine.

Question: Should sodium picosulfate as addition to fibers vs fibers alone be used for treatment of functional constipation?

Bibliography: Cassettari 2019

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium picosulfate + fibers	fibers	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events – not reported												
Defecation frequency - Dichotomous: number of patients having more than 3 bowel motions per week												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	15/16	9/15	RR: 1.56 (1.01 – 2.41) NNT: 3 (1 to 167)	336 more per 1000 (from 6 more to 847 more)	Low	
Painful defecation (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	1/16	4/15	RR: 0.23 (0.03 - 1.87)	205 fewer per 1000 (from 259 fewer to 232 more per 1000)	Low	
Stool consistency - Number of patients with Bristol Stool Form higher than Scale 1 or 2 (hard stools) (time of measurement: 8 weeks)												

1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	13/16	13/15	RR: 0.94 (0.69 - 1.28)	52 fewer per 1000 (from 269 fewer 243 more per 1000)	Low	
Fecal incontinence: number of patients with > 1 episode of fecal incontinence per week (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	2/16	5/15	RR: 0.38 (0.09 - 1.65)	207 fewer per 1000 (from 303 fewer to 217 more per 1000)	Low	
Abdominal pain (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	4/16	2/15	RR: 1.88 (0.40 - 8.78)	117 more per 1000 (from 80 fewer to 1000 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	0/16	0/17	Not estimable	Not estimable	Low	

[1]Downgraded two levels due to very serious imprecision

Liquid paraffin

1. Liquid paraffin vs herbal medicine (N=1)

Note: herbal medicine consisted of cassia fistula emulsion.

Question: Should liquid paraffin vs herbal medicine be used as treatment of functional constipation?

Bibliography: Mozaffarpur 2012

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Liquid paraffin**	**Herbal medicine**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 3 weeks)												

1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	17/40	31/41	RR: 0.56 (0.38 to 0.84)	333 less per 1000 (from 121 less to 469 less per 100)	Very low	
Withdrawals due to Adverse Events (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	1/40	0/41	RR: 3.07 (0.13 to 73.28)	52 more per 1000 (from 22 less to 1000 more per 1000)[4]	Very low	
Defecation frequency per week (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 34	N = 37		MD: 4.50 stools per week less (6.88 stools per week less to 2.12 stools per week more)	Very low	
Painful defecation: severity of pain on VAS 0-100 (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 34	N = 37		MD: 15.30 more pain during defecation on a scale of 0-100 (from 8.07 more pain to 22.53 more pain during defecation on a scale of 0-100)	Very low	
Stool consistency: VAS score (0-100), 0=soft stools (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 34	N = 37		MD: 13.50 harder stools on a scale of 0-100 (from 4.34 harder stools to 22.66 harder stools on a scale of 0-100)	Very low	
Fecal incontinence frequency per week (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N = 34	N = 37		MD: 0.20 more number of times fecal incontinence per week (from 0.45 less number of times fecal incontinence to 0.85 number of times more fecal incontinence per week)	Very low	
Serious adverse events (time of measurement: 3 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	0/40	0/41	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding and unclear randomization and allocation concealment

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to very sparse data and significant imprecision

[4]In order to interpret the results and calculate the absolute numbers a hypothetical event was added to the control group (1/41)

2. Liquid paraffin vs synbiotics (N=1)

Note: Synbiotics consisted of 1x10^9 CFU multispecies probiotics (L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis) and fructo-oligosaccharides.

Question: Should liquid paraffin vs synbiotics be used as treatment of functional constipation?

Bibliography: Khodadad 2010

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Liquid paraffin	Synbiotics	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	24/29	22/31	RR: 1.17 (0.88 - 1.54)	121 more per 1000 (from 85 less to 383 more per 1000)	Very low	
Withdrawals due to adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	0/29	0/31	Not estimable	Not estimable	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	N = 29	N = 31		MD: 1.53 higher (from 0.06 higher to 3.00 higher)	Very low	
Painful defecation (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	2/29	3/31	RR: 0.71 (0.13 - 3.96)	28 less per 1000 (from 84 less to 287 more per 1000)	Very low	
Stool consistency: Number of patients with hard stools (time of measurement: 4 weeks)												

1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	2/29	7/31	RR: 0.31 (0.07 - 1.35)	156 less per 1000 (from 210 less to 79 more per 1000)	Very low	
Fecal incontinence (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	N = 29	N = 31		MD: 0.18 higher (from 0.30 less to 0.66 more)	Very low	
Abdominal pain (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	4/29	2/31	RR: 2.14 (0.42 - 10.80)	74 more per 1000 (from 37 less to 632 more per 1000)	Very low	

[1]Downdgraded two levels due to unclear method of randomization, allocation and blinding

[2]Downgraded one level due to significant imprecision

Prucalopride

1. Prucalopride vs placebo (N=1)

Question: Should prucalopride vs placebo be used as treatment for functional constipation?

Bibliography: Mugie 2014

GRADE

Quality assessment							**No of patients**		**Effect**		**Certainty**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prucalopride**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	15/107	9/108	RR: 1.68 (0.77 – 3.68)	57 more per 1000 (19 fewer to 223 more)	Low	
Withdrawals due to Adverse Events (time of measurement: 8 weeks)												

1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	8/107	5/108	RR: 1.61 (0.55 – 4.78)	28 more per 1000 (21 fewer to 175 more)	Low	
Defecation frequency per week (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N = 106	N = 107		MD: 0.50 more stools per week (from 0.06 less stools per week to 1.06 more stools per week)	Moderate	
Painful defecation, change from baseline (scale 0-5), time of measurement 8 weeks												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Not serious	N = 106	N = 107		MD: 0.20 point less pain during defecation on a scale of 0-5 (from 0.51 point less pain to 0.11 point more pain during defecation on a scale of 0-5)	High	
Stool consistency: Bristol Stool Form Scale (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N = 106	N = 107		MD: 0.50 points softer stools on a scale of 0-7 (from 0.15 point softer stools to 0.85 softer stools on a scale of 0-7)	Moderate	
Fecal incontinence frequency per two weeks (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	N = 106	N = 107		MD: 5.20 less number of times fecal incontinence per 2 weeks (from 19.36 less to 8.96 more number of times fecal incontinence per 2 weeks)	Low	
Abdominal pain (scale 0-5) (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N = 106	N = 107		MD: 0.10 points less abdominal pain on a scale of 0-5 (from 0.33 points less to 0.13 point more abdominal pain on a scale of 0-5)	Moderate	
Serious adverse events (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	5/106	2/107	RR: 2.52 (0.50 - 12.72)	28 more per 1000 (from 9 less to 219 more per 1000)	Low	
Adverse events (time of measurement: 8 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	101/106	72/107	RR: 1.42 (1.23 - 1.63)	283 more per 1000 (from 155 more to 424 more per 1000)	Moderate	

[1]Downdgraded two levels due to very serious imprecision

[2]Downgraded one level due to significant imprecision

Lubiprostone

1. Lubiprostone vs placebo (N=1)

Question: Should lubiprostone vs placebo be used as treatment of functional constipation in children?

Bibliography: Benninga 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lubiprostone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Treatment success[1] (time of measurement: during 12 week treatment)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[2]	Not serious	74/404	28/202	RR: 1.32 (0.89 to 1.97)	44 more per 1000 (from 15 fewer to 134 more per 1000)	low	
Withdrawals due to Adverse Events (measured at 12 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[2]	Not serious	99/404	48/202	RR: 1.03 (0.76 to 1.39)	7 more per 1000 (from 57 less to 93 more per 1000)	Low	
Defecation frequency – reported as treatment success												
Painful defecation (scale 1-4) (measured at 12 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[3]	Not serious	N=395	N=199		MD: 0.21 higher on a scale of 1-4 for pain during defecation (from 0.01 lower to 0.43 higher on a scale of 1-4 for pain during defecation)	Moderate	
Fecal incontinence frequency per two weeks (measured at 12 weeks)												

1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Not serious	N=395	N=199		MD: 0.03 number of times less fecal incontinence per 2 weeks (from 0.11 number of times less to 0.05 number of times more fecal incontinence per 2 weeks)	High	
Abdominal pain (scale 1-4) (measured at 12 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Not serious	Not serious	N=395	N=199		MD: 0.07 points more abdominal pain on a scale of 1-4 (from 0.06 points less to 0.20 points more abdominal pain on a scale of 1-4)	High	
Serious adverse events												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[2]	Not serious	11/400	7/195	RR: 0.77 (0.30 - 1.95)	8 less per 1000 (from 25 less to 34 more per 1000)	Low	
Adverse events												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[2]	Not serious	239/400	114/195	RR: 1.02 (0.89 to 1.18)	12 more per 1000 (from 64 less to 105 more per 1000)	Low	

[1]Defined as: overall Spontaneous Bowel Movement (SBM) response, defined as an increase of 1 or more SBM/wk compared with baseline and 3 or more SBMs/wk for at least 9 weeks, including 3 of the final 4 treatment weeks.

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to serious imprecision

Linaclotide

1. Linaclotide vs placebo (N=1)

Question: Should linaclotide vs placebo be used for treatment of functional constipation?

Bibliography: Lorenzo 2020 (abstract only)[1], Di Lorenzo 2024

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linaclotide	placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 12 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	18/164	18/164	RR: 1.00 (0.54 to 1.85)	0 more per 1000 (from 50 less to 93 more per 1000)	Moderate	
Withdrawals due to Adverse Events (time of measurement range: 4 weeks to 12 weeks)												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	14/203	18/205	RR: 0.78 (0.40 to 1.52)	19 less per 1000 (from 53 less to 46 more per 1000)	Low	
Defecation frequency per week (time of measurement range: 4 to 12 weeks)												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N=203	N=205		MD: 0.94 higher (from 0.28 higher to 1.60 higher)	Moderate	
Stool consistency on the BSFS (scale 1-7) (time of measurement range: 4 weeks to 12 weeks)												
2	Randomised trials	Not serious	Serious[4]	Not serious	Very serious[3]	Not serious	N=198	N=198		MD: 0.10 lower (1.36 lower to 1.16 higher)	Very low	
Fecal incontinence - continuous: Change from baseline fecal incontinence daytime per day (time of measurement: 4 weeks)												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N=10	N=11		MD: 0.14 lower (from 0.33 lower to 0.05 higher)	Moderate	

Fecal incontinence – dichotomous: number of patients with fecal incontinence (time of measurement: 12 weeks)											
1	Randomised trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	38/164	36/164	RR: 1.06 (from 0.71 to 1.58)	RR: 13 more per 1000 (from 64 less to 127 more per 1000)	Moderate	
Abdominal pain on scale of 0-4 0=none, 4=a lot (time of measurement range: 4 weeks to 12 weeks)											
2	Randomised trials	Not serious	Serious[4]	Not serious	Serious[2]	Not serious	N=203	N=205		MD: 0.03 higher (from 0.46 lower to 0.52 higher)	Low	
Serious adverse events (time of measurement range: 4 weeks to 12 weeks)											
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	2/203	2/205	RR: 1.00 (0.14 to 7.01)	0 more per 1000 (from 8 less to 59 more per 1000)	Low	
Adverse events (time of measurement range: 4 weeks to 12 weeks)											
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	45/203	31/205	RR: 1.79 (0.68 to 4.69)	119 more per 1000 (from 48 less to 558 more per 1000)	Low	

[1]Study investigated different range of dosages for effectiveness and safety (phase 2 study). We only included data from high dose group (72 microgram), to combine data from Di Lorenzo 2024 paper which also used 72 microgram dosage.

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to serious imprecision

[4]Downgraded one level due to heterogeneity

Enema

1. Enema + PEG vs PEG (N=1)

Question: Should enemas as addition to PEG vs PEG alone be used for the treatment of functional constipation?

Bibliography: Bongers 2009

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enema + PEG	PEG	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 52 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	24/51	18/51	RR: 1.33 (0.83 – 2.14)	116 more per 1000 (60 fewer to 402 more)	Very low	
Withdrawals due to Adverse Events (time of measurement: 52 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	4/51	0/51	RR: 9.00 (0.50 - 162.97)	157 more per 1000 (from 10 less to 1000 more per 1000)	Very low	
Defecation frequency – no useful data (no SD reported)												
Painful defecation (time of measurement: 52 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	11/51	17/51	RR: 0.65 (0.34 to 1.24)	117 less per 1000 (from 220 less 80 more per 1000)	Very low	
Abdominal pain (time of measurement: 52 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	17/51	22/51	RR: 0.77 (0.47 to 1.27)	99 less per 1000 (229 less to 116 more per 1000)	Very low	

[1]Downgraded two levels due to high risk of performance and assessment bias and high risk of selective reporting.

[2]Added one fictional case to the control group in RevMan to calculate absolute numbers in order to better interpret results

Other

1. PEG + Domperidone vs PEG + Placebo (N=1)

Question: Should domperidone as addition to PEG vs PEG only be used for treatment of functional constipation?

Bibliography: Dehghani 2014

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEG + Domperidone	PEG + placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 6 months)												
1	Randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]		38/52	45/53	RR: 0.86 (0.70 – 1.05)	119 fewer per 1000 (254 fewer to 42 more)	Very low	
Withdrawals due to Adverse Events (time of measurement: 6 months)												
1	Randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]		5/52	2/53	RR: 2.55 (0.52 – 12.55)	58 more per 1000 (18 fewer to 437 more)	Very low	
Defecation frequency – dichotomous: number of patients that reported 3 or more episodes of defecation per week[1]												
1	randomised trials	Serious	Not serious	Not serious	Serious		47/52	44/53	RR 1.09 (0.94 – 1.27)	75 more per 1000 (50 less to 224 more)	Low	
Fecal incontinence: number of patients with ≥1 dirty underwear per week (time of measurement: 6 months)												
1	randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]		10/52	7/53	RR: 1.46 (0.60 – 3.35)	61 more per 1000 (from 53 less to 310 more per 1000)	Very low	
Adverse events (time of measurement: 6 months)												

1	Randomised trials	Serious[1]	Not serious	Not serious	Very serious[2]		0/52	0/52	Not estimable	Not estimable	Very low	

[1]Downgraded one level due to high risk of selective reporting

[2]Downgraded two levels due to very serious imprecision

[3]Outcome in study was reported as number of patients that reported ≤2 episodes of defecation per week. To compare with other studies the data is reported in this table as the number of patients that reported 3 or more episodes of defecation per week.

Appendix 6. GRADE tabellen niet-medicamenteuze behandeling

Probiotics

1. Probiotics vs placebo (N=8)

Notes: Zaja 2021 included only patients with anorexia nervosa. Wojtyniak 2017 included only children below 5 years of age. Lojanatorn 2023 included only children aged 1 – 5 years old.

Three studies investigated a mixture of different probiotics (Gan 2022, Tabbers 2011, Tjokronegoro 2020). Other studies investigated B. clausii (Lojanatorn 2023), L. Reuteri (Coccorullo 2010, Zaja 2021), and L. casei rhamnosus (Bu 2007, Wojtyniak 2017).ru

Question: Should probiotics vs placebo be used for functional constipation?

Bibliography: Lojanatorn 2023, Tabbers 2011, Tjokronegoro 2020, Zaja 2021, Bu 2007, Wojtyniak 2017, Gan 2022, Coccorullo 2010

GRADE

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 3 to 12 weeks)												
6	Randomised controlled trials	Serious[1]	Serious[2]	Not serious	Very serious[3]	Not serious	118/220	84/208	RR: 1.29 (0.89 to 1.85)	117 more per 1000 (from 44 less to 343 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (range: 3 weeks to 6 months)												
8	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[3]	Not serious	19/292	23/280	RR: 0.79 (0.44 to 1.40)	17 less per 1000 (from 46 less to 33 more per 1000)	Very low	
Defecation frequency per week (time of measurement range: 3 weeks to 6 months)												
5	Randomised controlled trials	Serious[1]	Serious[2]	Not serious	Serious[4]	Not serious	N=192	N=180		MD: 0.32 stools more per week (from 1.12 stools less per week to 1.76 stools more per week)	Very low	
Painful defecation frequency per week (time of measurement range: 4 weeks)												

2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Not serious	Not serious	N=61	N=60		MD: 0.05 higher (from 0.25 lower to 0.35 higher)	Moderate	
Painful defecation – dichotomous: number of patients with painful defecation (time of measurement range: 3 to 4 weeks)												
2	Randomised controlled trials	Not serious	Serious[2]	Not serious	Very serious[3]	Not serious	44/118	50/119	RR: 0.74 (0.27 to 2.02)	109 less per 1000 (from 307 less to 429 more per 1000)	Very low	
Stool consistency – mean score on Bristol Stool form Scale (1= very hard, 7=very loose) (time of measurement: 4 weeks)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Not serious	Not serious	N=61	N=58		MD: 0.16 lower (from 0.49 lower to 0.16 higher)	Moderate	
Stool consistency – dichotomous: number of patients with normal stool consistency (time of measurement range: 1 to 6 months)												
2	Randomised controlled trials	Not serious	Serious[2]	Not serious	Very serious[3]	Not serious	39/54	31/55	RR: 1.19 (0.64 to 2.20)	107 more per 1000 (from 203 less to 677 more per 1000)	Very low	
Fecal incontinence – dichotomous: number of patients with fecal incontinence episodes (time of measurement range: 3 to 4 weeks)												
2	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	29/118	43/119	RR: 0.61 (0.27 to 1.38)	141 less per 1000 (from 264 less to 137 more per 1000)	Low	
Fecal incontinence frequency per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	N=41	N=40		MD: not estimable	Low	
Abdominal pain – number of patients with abdominal pain (time of measurements: 3 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	43/79	40/80	RR: 1.09 (0.81 to 1.47)	45 more per 1000 (from 95 less to 235 more per 1000)	Low	
Serious adverse events (time of measurements range: 3 weeks to 6 months)												
4	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[3]	Not serious	0/123	0/119	Not estimable	Not estimable	Low	

Adverse events (time of measurements range: 3 weeks to 6 months)												
5	Randomised controlled trials	Serious[1]	Not serious	Not serious	Serious[4]	Not serious	9/202	16/199	RR: 0.59 (0.24 to 1.44)	33 less per 1000 (61 less to 35 more per 1000)	low	

[1]Downgraded one level due to unclear selective reporting and unclear allocation concealment in several studies and high risk of performance and assessment bias in one study.
[2]Downgraded one level due to serious heterogeneity
[3]Downgraded two levels due to very serious imprecision
[4]Downgraded one level due to significant imprecision

2. Probiotics vs laxatives (N=3)

Notes: Did not use data from Kubota 2020 because def frequency was reported as "Change from baseline in Bowel movements per week, least square mean (95% CI)", saw that in probiotics SR Kubota was also not included in meta-analysis.
Number of withdrawals was very high in Lee 2022 (IG: 22 lost to follow-up, 23 drug change (could be due to poor treatment outcome, poor compliance, and/or other side effects), CG: 44 lost to follow-up, 3 drug change).
Bu 2007 compared L. casei rhamnosus lcr35 to magnesiumoxide. Lee 2022 compared S. boulardii to lactulose. Olgaç 2013 compared L. reuteri to lactulose.
Question: Should probiotics vs laxative be used for functional constipation?
Bibliography: Bu 2007, Lee 2022, Olgaç 2013

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Probiotics**	**Laxative**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement range: 4 to 12 weeks)												
2	Randomised controlled trials	Very serious[1]	Very serious	Not serious	Very serious[2]	Not serious	18/68	31/87	RR: 0.61 (0.12 to 2.96)	139 less per 1000 (from 314 less to 698 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (range: 4 to 12 weeks)												

3	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	51/93	55/115	RR: 1.30 (1.08 to 1.56)	143 more per 1000 (38 more 268 more per 1000)	Very low	
Defecation frequency per week (time of measurement range: 2 to 4 weeks)												
3	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=82	N=106		MD: 0.36 stools more per week (0.15 stools more per week to 0.57 stools more per week)	Low	
Painful defecation – frequency per week (Lee 2022) (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=39	N=60		MD: 0.20 higher (from 0.07 lower to 0.47 higher)	Low	
Stool consistency: BSFS (time of measurement range: 2 to 4 weeks)												
2	Randomised controlled trials	Very serious[1]	Serious[3]	Not serious	Not serious	Not serious	N=62	N=88		MD: 0.17 lower (from 0.61 lower to 0.26 higher)	Very low	
Stool consistency: percentage of hard stools (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious	Not serious	Not serious	Not serious	Not serious	N=18	N=18		MD: 1.10 lower (from 8.81 lower to 6.61 higher)	Low	
Fecal incontinence frequency per week (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	N= 37	N=60		MD: 0.43 higher (from 0.82 lower to 1.68 higher)	Very low	
Adverse events (Kubota, olgac) (time of measurements range: 4 to 12 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/45	0/49	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding, unclear allocation concealment and high risk of attrition bias

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to significant heterogeneity I^2=73%

3. Additional effect: Probiotics + laxative vs laxative (N=9)

Notes: included PEG and Lactulose as laxatives. Did not use data from Kubota 2020 (yet) because defecation frequency was reported as "Change from baseline in Bowel movements per week, least square mean (95% CI)" and could not be included in the meta-analysis.

Question: Should probiotics in addition to a laxative vs laxative only be used for functional constipation?

Bibliography: Abediny 2016, Banaszkiewicz 2005, Foroughi 2022, Jadrešin 2018, Lee 2022, Kubota 2020, Russo 2017, Wegner 2018, Sadeghzadeh 2014

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics + laxative	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 8 to 12 weeks)												
4	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	86/156	74/153	RR: 1.08 (0.87 to 1.34)	25 more per 1000 (from 40 less to 104 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement range: 4 to 12 weeks)												
6	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	49/247	58/242	RR: 0.71 (0.24 to 2.07)	70 less per 1000 (from 182 less to 256 more per 1000)	Very low	
Defecation frequency per week (time of measurement range:)												
5	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=188	N=190		MD: 0.12 stools more per week (0.09 lower stools per week to 0.34 higher)	Low	
Painful defecation frequency per week (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Not serious	Not serious	N=61	N=60		MD: 0.16 higher (from 0.11 lower to 0.43 higher)	Low	

Painful defecation – dichotomous: number of children with painful defecation (time of measurement: 8 weeks)											
1	Randomised controlled trials	Very serious[4]	Not serious	Not serious	Serious[5]	Not serious	13/65	8/64	RR: 1.60 (0.71 to 3.60)	75 more per 1000 (from 36 lower to 325 more per 1000)	Very Low	
Stool consistency – continuous: BSFS and scale 1-3 (low is hard stools, high is soft stools) (time of measurement range: 4 to 12 weeks)											
3	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Not serious	Not serious	N=110	N=109		SMD: 0.18 higher (from 0.09 lower to 0.45 higher)	Low	
Stool consistency – dichotomous (time of measurement: 4 to 8 weeks)											
2	Randomised controlled trials	Very serious[3]	Serious[6]	Not serious	Serious[5]	Not serious	12/110	11/109	RR: 1.06 [0.33, 3.36]	6 more per 1000 (from 68 less to 238 more per 1000)	Very Low	
Fecal incontinence frequency per week (time of measurement: 2 to 12 weeks)											
2	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Not serious	Not serious	N=104	N=101		MD: 0.26 higher (from 0.20 lower to 0.72 higher)	Very low	
Fecal incontinence – dichotomous (time of measurement: 8 weeks)											
2	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Serious[5]	Not serious	19/84	12/86	RR: 1.63 (0.85 to 3.09)	88 more per 1000 (from 21 less to 292 more per 1000)	Very low	
Abdominal pain – dichotomous (time of measurement: 4 to 8 weeks)											
3	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Very serious[2]	Not serious	27/135	43/134	RR: 0.64 (0.43 to 0.96) NNT: 9 (5 to 78)	116 less per 1000 (from 183 less to 13 less per 1000)	Very low	
Serious adverse events (time of measurement: 8 weeks)											
1	Randomised controlled trials	Very serious[4]	Not serious	Not serious	Very serious[2]	Not serious	0/65	0/64	Not estimable	Not estimable	Very low	
Adverse events (time of measurements range: 4 to 12 weeks)											
4	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Serious[5]	Not serious	6/173	8/173	RR: 0.72 (0.26 to 1.98)	13 less per 1000 (from 34 less to 45 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding, high risk of attrition bias and selective reporting, and unclear allocation concealment
[2]Downgraded two levels due to very serious imprecision
[3]Downgraded two levels due to lack of blinding, high risk of attrition bias and unclear allocation concealment
[4]Downgraded two levels due to unclear allocation concealment and unclear blinding.
[5]Downgraded one level due to significant imprecision
[6]Downgraded one level due to heterogeneity I^2=57%

4. Additional effect: probiotics + diet with goat yoghurt vs diet with goat yoghurt (N=1)

Question: Should probiotics as addition to goat yoghurt vs goat yoghurt be used for functional constipation?
Bibliography: Guerra 2011

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics + goat yoghurt	Goat yoghurt	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to AE (time of measurement: 5 weeks)												
1	Randomised controlled trials	Serious	Not serious	Not serious	Very serious	Not serious	1/30	0/30	RR: 3.00 (0.13 to 70.83)	67 more per 1000 (from 29 less to 1000 more per 1000)	Very low	
Defecation frequency – no data reported												

[1]Downgraded one level due to unclear allocation concealment and selective reporting

5. Formula 1 intact protein + probiotic + PEG vs Formula 2 hydrolyzed whey + PEG (N=1)

Notes: included children aged 12 to 32 months. Compared two different formulas. Formula 1 (intervention) contained intact protein and a probiotic. Formula 2 (control) contained hydrolyzed whey protein. Both groups also received PEG.

Question: Should formula with intact protein and a probiotic vs formula with hydrolyzed whey protein in addition to PEG be used for the treatment of functional constipation

Bibliography: Sevilla 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Formula 1**	**Formula 2**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 8 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	43/47	38/48[3]	RR: 1.16 (0.98 to 1.37)	127 more per 1000 (from 16 less to 293 more per 1000)	Very low	
Withdrawals due to Adverse Events (time of measurement: 8 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	2/47	0/48	RR: 5.10 (0.25 to 103.57)	86 more per 1000 (from 16 less to 1000 more per 1000)[2]	Very low	
Defecation frequency per week (time of measurement: mean week 1-8)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=47	N=48		MD: 0.06 lower (from 1.54 lower to 1.42 higher)	Low	
Painful defecation – dichotomous: number of patients (time of measurement: 8 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious	Not serious	6/47	6/48	RR: 1.02 (0.35 to 2.94)	3 more per 1000 (from 81 less to 243 more per 1000)	Very low	
Stool consistency – dichotomous: number of subjects with a hard stool on one or more occasions throughout week 5-8												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	10/47	14/48	RR: 0.73 (0.36 to 1.48)	79 less per 1000 (from 187 less to 140 more per 1000)	Very low	

Fecal incontinence – dichotomous: number of subjects with fecal incontinence throughout week 5-8[4]												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	10/47	14/48	RR: 0.73 (0.36 to 1.48)	79 less per 1000 (from 187 less to 140 more per 1000)	Very low	
Serious adverse events (time of measurement: 8 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	0/47	0/48	Not estimable	Not estimable	Very low	
Adverse events (time of measurement: 8 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious	Not serious	0/47	0/48	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding and unclear allocation concealment

[2]Added 1 fictional event to Formula 2 group to calculate absolute numbers

[3]Please note the very high success numbers in both groups. This could indicate that PEG is effective in children aged 1 to 2,5 years old.

[4]Please note that fecal incontinence can be considered as an invalid outcome in such young children.

Herbal medicine

1. Herbal medicine vs laxative (N=8)

Notes: Herbal medicines consisted of Black Strap Molasses, Cassia fistula, LaxaPlus Barij®, flixweed (D. Sophia seed), Golghand®, and Viola Flower Syrup, R. damascena and brown sugar. Mozaffarpur 2012 compared herbal medicine to liquid paraffin, all other studies compared herbal medicine to PEG.
Question: Should herbal medicine vs laxative be used for functional constipation?
Bibliography: Dehghani 2019, Esmaeilidooki 2016, Imanieh 2022, Nasri 2022, Nimrouzi 2015, Saneian 2021, Tavassoli 2021, Mozaffarpur 2012

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herbal mediicne	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 3 to 8 weeks)												
5	Randomised controlled trials	Serious[1]	Serious[4]	Not serious	Serious[2]	Not serious	191/248	176/254	RR: 1.11 (0.92 to 1.34)	76 more per 1000 (from 55 less to 236 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (range: 3 to 8 weeks)												
8	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[3]	Not serious	7/408	12/414	RR: 0.63 (0.26 to 1.53)	14 less per 1000 (from 27 less to 20 more per 1000)	Very low	
Defecation frequency per week (time of measurement range: 3 to 8 weeks)												
5	Randomised controlled trials	Serious[1]	Serious[4]	Not serious	Serious[2]	Not serious	N=242	N=237		MD: 1.72 stools more per week (0.23 stools less per week to 3.67 stools more per week)[7]	Very low	
Painful defecation – dichotomous: number of patients with painful defecation (time of measurement: 8 weeks)												
2	Randomised controlled trials	Very serious[5]	Not serious	Not serious	Serious[2]	Not serious	28/90	25/90	RR: 1.11 (0.70 to 1.75)	31 more per 1000 (from 83 less to 208 more per 1000)	Very low	
Painful defecation – continuous: painful defecations per week (time of measurement: 3 to 4 weeks)												

2	Randomised controlled trials	Serious[6]	Serious[4]	Not serious	Serious[2]	Not serious	N=123	N=119		MD: 0.10 higher (from 0.52 lower to 0.71 higher)	Very low	
Painful defecation – pain severity on a VAS-scale (0-100) (time of measurement range: 3 to 4 weeks)												
2	Randomised controlled trials	Serious[6]	Serious[4]	Not serious	Serious[2]	Not serious	N=89	N=91		MD: 8.19 lower (from 21.40 lower to 5.02 higher)	Very low	
Stool consistency – frequency of hard stools per week (time of measurement range: 3 to 4 weeks)												
2	Randomised controlled trials	Very serious[4]	Serious[4]	Not serious	Serious[2]	Not serious	N = 119	N = 123		MD: 0.45 lower (from 1.39 lower to 0.49 higher)	Very low	
Stool consistency - reported on VAS score (0-100), 0=soft (time of measurement range: 3 to 4 weeks)												
2	Randomised controlled trials	Very serious[4]	Serious[4]	Not serious	Serious[2]	Not serious	N=89	N=91		MD: 8.44 lower (from 16.77 lower to 0.11 lower)	Very low	
Fecal incontinence frequency per week (time of measurement range: 3 to 4 weeks)												
4	Randomised controlled trials	Very serious[4]	Not serious	Not serious	Serious[2]	Not serious	N=212	N=210		MD: 0.43 lower (from 1.39 lower to 0.52 higher)	Very low	
Adverse events (time of measurement: 4 weeks)												
3	Randomised controlled trials	Serious[6]	Not serious	Not serious	Very serious[3]	Not serious	20/164	39/179	RR: 0.49 (0.15 to 1.60)	111 less per 1000 (from 185 less to 131 more per 1000)	Very low	

[1]Downgraded one level due to open label studies, high risk selective reporting, high risk for other bias

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to very serious imprecision

[4]Downgraded one level due to significant heterogeneity. Could be explained by the different types of herbal medicine and/or different types of laxatives.

[5]Downgraded two levels due to high risk performance and assessment bias, and high risk selective reporting

[6]Downgraded one level due to open label studies

[7]Sensitivity analysis for only Esmaeilidooki 2016 and Mozaffarpur 2012 (both Cassia fistula as intervention), led to a significant difference favoring Cassia fistula (MD 4.22 higher, 95% CI 2.78 higher to 5.66 higher per week). However evidence would be low/very low (very serious RioB).

2. Herbal medicine vs placebo (N=1)

Note: Cai 2018 investigated Xiao'er Biantong granules

Question: Should herbal medicine vs placebo be used for functional constipation?

Bibliography: Cai 2018

GRADE

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Herbal medicne	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	195/360	4/120	RR: 16.25 (6.17 to 42.79)	508 more per 1000 (from 172 more to 1000 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	33/360	16/120	RR 0.69 (0.39 to 1.20)	41 less per 1000 (from 81 less to 27 more per 1000)	Very low	
Defecation frequency – dichotomous: number of children with ≥3 bowel movements per week (time of measurement range: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	291/360	34/120	RR 2.85 (2.14 to 3.81)	524 more per 1000 (from 323 more to 796 more per 1000)	Low	
Stool consistency – Disappearance rate of dry stool (type 1 and 2 Bristol Stool Scale)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	236/360	11/120	RR 7.15 (4.05 to 12.62)	564 more per 1000 (from 280 more to 1000 more per 1000)	Very low	
Fecal incontinence frequency per week (time of measurement range: 3 to 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	3/5	0/3	RR 4.67 (0.32 to 68.03)	1000 more per 1000 (from 227 less to 1000 more per 1000)[3]	Very low	

Adverse events												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	7/360	2/120	RR 1.17 (0.25 to 5.54)	3 more per 1000 (from 13 less to 76 more per 1000)	Very low	

[1]Downgraded two levels due to unclear risk of attrition bias and selecting reporting

[2]Downgraded two levels due to significant imprecision

[3]Inserted a fictional event (1/3) for placebo in Revman to calculate absolute numbers.

Fibers

1. Fiber vs placebo (N=3)

Notes: Outcome data from Loening-Baucke 2004 were not included, because no data pre cross-over was available. The study compared Glucomannan fiber to placebo (4 weeks treatment and then cross-over, without washout period).
Weber 2014 investigated mixture of several fibers and reported in their methods that "It should be emphasized that several of the components (10.5% fructooligosaccharides, 12.5% inulin, 24% gum arabic, 9% resistant starch, 33% soy polysaccharide, and 12% cellulose) are considered prebiotics."
Question: Should fiber vs placebo be used for functional constipation?
Bibliography: Chmielewska 2011, Weber 2014, Loening-Baucke 2004

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fiber	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	36/67	39/70	RR: 1.00 (0.74 to 1.35)	0 more per 1000 (from 145 less to 195 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 4 weeks)												
3	Randomised controlled trials	Serious	Not serious	Not serious	Very Serious	Not serious	11/94	11/89	RR: 0.78 (0.37 to 1.65)	27 less per 1000 (from 78 less to 80 more per 1000)	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
2	Randomised controlled trials	Serious	Very serious	Not serious	Serious	Not serious	N=62	N=64		SMD: 1.37 higher (0.21 lower to 2.95 higher)	Very low	
Painful defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious	Not serious	Not serious	Very serious	Not serious	N=36	N=36		MD: not estimable	Very low	

Stool consistency BSFS 4-7 were scored as non hardened stool (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	12/27	4/30	RR: 3.33 (1.22 to 9.11)	311 more per 1000 (from 29 more to 1000 more per 1000)	Very low	
Stool consistency BSFS (1-7) (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious	Not serious	Not serious	Not serious	Not serious	N=36	N=36		MD: 0.10 lower (from 0.59 lower to 0.39 higher)	Moderate	
Abdominal pain frequency episodes per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious	Not serious	Not serious	Not serious	Not serious	N=36	N=36		MD: 0.00 (from 0.54 lower to 0.54 higher)	Moderate	
Serious adverse events (time of measurement: 4 weeks)												
3	Randomised controlled trials	Serious	Not serious	Not serious	Very serious	Not serious	1/94	0/89	RR: 3.00 (from 0.13 to 71.51)	Not estimable	Very low	
Adverse events (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[3]	Not serious	Not serious	Very serious	Not serious	0/27	0/19	Not estimable	Not estimable	Very low	

[1]Downgraded one level due to unclear allocation concealment and selective reporting in one study

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded two levels due to unclear risk of bias in almost every domain

2. Fiber vs laxative (N=4)

Notes: Cassetari 2018 investigated the laxatives PEG and sodium picosulfate[5]. The comparison of Green Banana Biomass vs Sodium Picosulfate was not included, because then the Green Banana Biomass group would be included twice in the overall comparison of fiber vs laxative.
Kokke 2018 compared a fiber mixture to lactulose. Quitadamo 2012 compared a fiber mixture to PEG. Üstündağ 2010 compared partially hydrolysed guargum to lactulose.
Question: Should fiber vs laxative be used for functional constipation?
Bibliography: Cassetari 2018, Kokke 2008, Quitadamo 2012, Üstündağ 2010

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fiber	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 8 weeks)												
1	Randomsied controlled trial	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	28/50	38/50	RR: 0.74 (0.55 to 0.99)	197 less per 1000 (from 342 less to 8 less per 1000)	Very low	
Withdrawals due to Adverse Events at study end (range: 4 - 8 weeks)												
3	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	6/155	5/148	RR: 1.16 (0.37 to 3.62)	5 more per 1000 (from 21 less to 89 more per 1000)	Very low	
Defecation frequency per week (time of measurement range: 4 - 8 weeks)												
2	Randomsied controlled trials	Very serious[1]	Serious	Not serious	Serious[4]	Not serious	N=67	N=77		MD: 0.63 stools less per week (1.41 stools less per week to 0.15 stools more per week)	Very low	
Defecation frequency – dichotomous: number of patients having more than 3 bowel motions as week (time of measurement: 8 weeks)												
1	Randomsied controlled trials	Serious[3]	Not serious	Not serious	Very serious[2]	Not serious	9/15	8/17	RR: 1.27 (0.66 to 2.45)	127 more per 1000 (from 160 less to 682 more per 1000)	Very low	

Painful defecation – number of patients reporting painful stools (time of measurement; 8 weeks)												
1	Randomsied controlled trials	Serious[3]	Not serious	Not serious	Very serious[2]	Not serious	4/15	4/16	RR: 1.07 (0.32 to 3.52)	17 more per 1000 (from 170 less to 630 more per 1000)	Very low	
Fecal incontinence - number of patients with 1 or more fecal incontinence episodes per week (time of measurement; 8 weeks)												
1	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Serious[4]	Not serious	9/70	5/70	RR: 1.80 (0.64 to 5.10)	57 more per 1000 (from 26 less to 293 more per 1000)	Very low	
Fecal incontinence frequency per week (time of measurement; 8 weeks)												
1	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=36	N=47		MD: 0.10 higher (from 0.42 lower to 0.62 higher)	Low	
Abdominal pain – number of patients with abdominal pain (time of measurement; 4 - 8 weeks)												
3	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Serious[4]	Not serious	15/86	14/97	RR: 1.21 (0.63 to 2.33)	30 more per 1000 (from 53 less to 192 more per 1000)	Very low	
Serious adverse events (time of measurement; 8 weeks)												
2	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/80	0/86	Not estimable	Not estimable	Very low	
Adverse events (time of measurement; 8 weeks)												
3	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/116	0/133	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding and unclear allocation concealment and risk of selective reporting

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to unclear allocation concealment

[4]Downgraded one level due to significant imprecision

[5]Now only included comparison of Green Banana Biomass vs PEG, because there is also another study comparing fiber vs PEG. The comparison of GBB vs sodium picosulfate was also made in Cassetari. However both laxatives were compared to the same GBB group, so including both comparisons would cause that the GBB group would be included twice in the comparison of Fiber vs Laxative. The comparison of GBB vs sodium picosulfate is discussed separately in the pharma part.

Prebiotics

1. Prebiotics vs placebo (N=1)

Note: the study only included children aged 6 months to 24 months old.

Question: Should prebiotics vs placebo be used for functional constipation?

Bibliography: Da Silva Souza 2018

GRADE

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prebiotics	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	15/19	10/19	RR: 1.50 (0.92 to 2.44)	263 more per 1000 (from 42 less to 758 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Very serious	Very serious[2]	Not serious	1/19	0/19	RR: 3.00 (0.13 to 69.31)	105 more per 1000 (from 46 less to 1000 more per 1000)[3]	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Not serious	Not serious	N=18	N=18		MD: 0.22 stools more per week (0.70 stools less per week to 1.14 stools more per week)	Low	
Painful defecation - % of bowel movements (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Serious	Not serious	N=18	N=18		MD: 13.71 lower (from 37.99 lower to 10.57 more)	Low	
Stool consistency - % of BMs with soft stool (time of measurement: 4 weeks)												

1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	N=18	N=18		MD: 18.00 higher (from 3.58 lower to 39.58 more)	Very low	
Adverse events (time of measurement: 4 weeks)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	4/19	0/19	RR: 9.00 (0.52 to 156.41)	157 more per 1000 (from 27 less to 1000 more per 1000)[3]	Very low	

[1]Downgraded one level due to unclear allocation concealment

[2]Downgraded two levels due to very serious imprecision

[3]Added fictional event to control group to obtain absolute numbers, in order to better interpret results.

2. Prebiotics vs laxative (N=1)

Question: Should prebiotics vs laxatives be used for functional constipation?

Bibliography: Foroughi 2022

GRADE

See GRADE tables for pharmacological maintenance treatment

3. Prebiotics + probiotics vs laxative (N=1)

Question: Should prebiotics in combination with probiotics vs laxatives be used for functional constipation?

Bibliography: Foroughi 2022

GRADE

See GRADE tables for pharmacological maintenance treatment

4. Formula with prebiotics + hydrolyzed whey protein vs standard formula (N=2)

Notes: Bongers 2007, children were aged 3 – 20 weeks. Savino 2005, children were aged max 16 weeks old.

Question: Should formula with prebiotics and hydrolyzed whey protein vs standard formula be used for functional constipation?

Bibliography: Bongers 2007, Savino 2005

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Formula with prebiotics + hydrolyzed whey protein	Standard formula	Relative (95% CI)	Absolute		
Treatment success (time of measurement range:) – not reported												
Withdrawals due to Adverse Events at study end (range: 2 -3 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/89	1/69	RR: 0.25 (0.01 to 5.83)	11 less per 1000 (from 14 less to 70 more per 1000)	Very low	
Defecation frequency (time of measurement range: 2 - 3 weeks)												
2	Randomised controlled trials	Very serious[2]	Not serious	Not serious	Serious	Not serious	N=75	N=55		SMD: 0.38 higher (0.03 higher to 0.73 higher)	Very low	
Painful defecation – number of patients with painful stools (time of measurement: 3 weeks)												
1	Randomised controlled trials	Serious[3]	Not serious	Not serious	Very serious[2]	Not serious	13/20	10/15	RR: 0.97 (0.60 to 1.58)	20 less per 1000 (from 280 less to 387 more per 1000)	Very low	
Stool consistency - number of patients with formed tools (on scale of hard/formed/runny) (time of measurement range: 2-3 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	18/69	17/54	RR: 1.29 (0.79 to 2.10)	91 more per 1000 (from 66 less to 346 more per 1000)	Very low	

Serious adverse events (time of measurement range: 2-3 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/89	0/69	Not estimable	Not estimable	Very low	
Adverse events (time of measurement range: 2-3 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/89	0/69	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to lack of blinding and unclear risks of selective reporting and attrition bias

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to unclear allocation concealment and unclear risk of selective reporting

Synbiotics

1. Synbiotics vs placebo (N=1)

Question: Should synbiotics vs placebo be used for functional constipation?

Bibliography: Baştürk 2017

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Synbiotics	Placebo	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised controlled trial	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	48/77	21/78	RR: 2.32 (1.54 to 3.47) NNT: 3 (2 to 7)	355 more per 1000 (from 145 more to 665 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 4 weeks)												
1	Randomised controlled trial	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	5/77	4/78	RR: 1.27 (0.35 to 4.54)	14 more per 1000 (from 33 less to 182 more per 1000)	Very low	
Defecation frequency per week (time of measurement range:) – not adequately reported												
Painful defecation – number of patients (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	16/77	27/78	RR: 0.60 (0.35 to 1.02)	138 less per 1000 (from 225 less to 7 more per 1000)	Very low	
Stool consistency – not adequately reported												

Fecal incontinence – not adequately reported												
Abdominal pain – number of patients (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	4/77	41/78	RR: 0.10 (0.04 to 0.26)	473 less per 1000 (from 505 less to 389 less per 1000)	Low	
Adverse events (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	0/77	0/78	Not estimable	Not estimable	Very low	

[1]Downgraded two levels due to unclear randomization methods and unclear risk of attrition and selective reporting bias

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to very serious imprecision

2. Synbiotics vs laxative (N=1)

Question: Should synbiotics vs laxatives be used for functional constipation?
Bibliography: Khodadad 2010

GRADE

See GRADE tables for pharmacological maintenance treatment

3. Additional effect: synbiotics + laxative vs laxative (N=1)

Question: Should synbiotics as addition to laxatives vs laxatives alone be used for functional constipation?
Bibliography: Khodadad 2010

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Synbiotics + laxative	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	28/37	24/29	RR: 0.91 (0.71 to 1.17)	74 less per 1000 (from 240 less to 141 more per 1000)	Very low	
Withdrawals due to adverse events (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/37	0/29	Not estimable	Not estimable	Very low	
Defecation frequency per week (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Not serious[2]	Not serious	N=37	N=29		MD: 0.02 higher (from 0.56 lower to 0.60 higher)	Low	
Painful defecation (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	4/37	2/29	RR: 1.57 (0.31 to 7.97)	39 more per 1000 (from 48 less to 481 more per 1000)	Very low	

Stool consistency: Number of patients with hard stools (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	4/37	2/29	RR: 1.57 (0.31 to 7.97)	39 more per 1000 (from 48 less to 481 more per 1000)	Very low	
Fecal incontinence (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	N=37	N=29		MD: not estimable	Very low	
Abdominal pain (time of measurement: 4 weeks)												
1	Randomised trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	5/37	4/29	RR: 0.98 (0.29 to 3.32)	3 less per 1000 (from 98 less to 320 more per 1000)	Very low	

[1]Downdgraded two levels due to unclear method of randomization, allocation and blinding

[2]Downgraded two levels due to very serious imprecision

4. Probiotics + prebiotics (synbiotics) vs prebiotics (N=1)

Question: Should probiotics as addition to prebiotics (synbiotics) vs prebiotics alone be used for functional constipation?
Bibliography: Foroughi 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Synbiotics	Probiotics	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to AE – not reported												
Defecation frequency per week (time of measurement: 3 weeks)												
1	Randomised controlled trial	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=36	N=36		MD: 0.66 higher (from 0.32 higher to 1.00 higher)	Low	
Painless bowel movements frequency per week												
1	Randomised controlled trial	Very serious[1]	Not serious	Not serious	Not serious	Not serious	N=36	N=36		MD: 0.69 higher (from 0.05 higher to 1.33 higher)	Low	

[1]Downgraded two levels due to unclear randomization and allocation concealment and unclear attrition and selective reporting

Biofeedback

1. Additional effect: biofeedback + laxative vs laxative (N=3)

Question: Should biofeedback as addition to a laxative vs laxative only be used for functional constipation?

Bibliography: Loening-Baucke 1990, Sunic-Omejc 2002, Van der Plas 1996

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biofeedback + laxative	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: 6 weeks to 7 months)												
3	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	64/146	47/138	RR: 1.36 (0.75 to 2.47)	122 more per 1000 (from 85 less to 500 more per 100)	Very low	
Withdrawals due to Adverse Events at study end (time of measurement range: 12 weeks to 18 months)												
3	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	6/146	2/138	RR: 2.44 (0.58 to 10.28)	21 more per 1000 (from 6 less to 134 more per 100)	Very low	
Defecation frequency per week: not reported												
Fecal incontinence frequency per week (time of measurement: 7 months)												
1	Randomsied controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	N=22	N=19		2.00 lower (from 4.73 lower to 0.73 higher)	Very low	

[1]Downgraded two levels due to unclear randomization methods, allocation methods and unclear or high risk selective reporting

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to serious imprecision

2. Biofeedback vs no biofeedback (N=1)

Notes: no description of the control group, just 'no biofeedback'

Question: Should biofeedback vs no biofeedback be used for functional constipation?

Bibliography: Castilla 2021 (abstract only)

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biofeedback	No biofeedback	Relative (95% CI)	Absolute		
Treatment success (time of measurement range: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	10/12	4/12	RR: 2.50 (1.08 to 5.79)	500 more per 1000 (from 27 more to 1000 per 1000 more)	Very low	
Withdrawals due to Adverse Events at study end – not reported												
Defecation frequency per week – not reported												

[1]Downgraded two levels due to unclear randomization methods, allocation concealment, blinding and selective reporting

[2]Downgraded wo levels due to serious imprecision

3. Biofeedback at home + laboratory vs biofeedback in laboratory (N=1)

Question: Should biofeedback at home in addition to laboratory feedback vs biofeedback in laboratory only be used for functional constipation?
Bibliography: Croffie 2005

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biofeedback at home + laboratory	Laboratory	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 months)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	10/12	22/24	RR: 0.91 (0.69 to 1.20)	83 less per 1000 (284 less to 183 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end – not reported												
1												
Defecation frequency per week: not reported – not adequately reported												
1												
Fecal incontinence – not adequately reported												
1												

[1]Downgraded two levels due to unclear randomization methods, allocation concealment and selective reporting
[2]Downgraded two levels due to serious imprecision

Nerve stimulation

1. Parasacral transcutaneous electrical nerve stimulation vs sham therapy (N=1)

Notes: Treatment with parasacral transcutaneous electrical nerve stimulation (PTENS) consisted of 20 minute sessions, 3 times a week for a total of 20 sessions. The control group received sham therapy. Both groups received standard urotherapy, because the included patients were diagnosed with functional constipation associated with lower urinary tract symptoms (LUTS).

Question: Should parasascral transcutaneous electrical nerve stimulation vs sham therapy be used for functional constipation?

Bibliography: de Abreu 2021

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PTENS	Sham	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 7-9 weeks)												
1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Serious[3]	Not serious	16/20	6/20	RR: 2.67 (1.32 to 5.39) NNT: 2 (1 to 10)	501 more per 1000 (from 96 more to 1000 more per 1000)	Low	
Withdrawals due to Adverse Events at study end (time of measurement: 7-9 weeks)												
1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/20	0/20	Not estimable	Not estimable	Very low	
Defecation frequency - dichotomous: two or more bowel movements per week (time of measurement: 7-9 weeks)												
1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	19/20	13/20	RR: 1.46 (1.04 to 2.05) NNT: 3 (1 to 38)	299 more per 1000 (from 26 more to 683 more per 1000)	Very low	
Painful defecation - Number of patients with pain/straining during defecation after treatment (time of measurement: 7-9 weeks)												

1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	6/20	10/20	RR: 0.60 (0.27 to 1.34)	200 less per 1000 (from 365 less to 170 more per 1000)	Very low	
Stool consistency - number of patients with stool type 1 or 2 on Bristol Stool Scale (hard) after treatment (time of measurement: 7-9 weeks)												
1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	5/20	10/20	RR: 0.50 (0.21 to 1.20)	250 less per 1000 (from 395 less to 100 more per 1000)	Very low	
Fecal incontinence - Episode of fecal incontinence after treatment (time of measurement: 7-9 weeks)												
1	Randomised controlled trial	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/20	4/20	RR: 0.50 (0.10 to 2.43)	100 less per 1000 (from 180 less to 286 more per 1000)	Very low	

[1]Downgraded one level due to selective reporting, because no safety outcome was reported
[2]Downgraded two levels due to very serious imprecision
[3]Downgraded one level due to serious imprecision

2. Abdominal transcutaneous electrical stimulation vs sham therapy (N=1)

Notes: Children were diagnosed with FC based on the Rome II criteria and diagnosed with slow transit constipation. Treatment consisted of 12x20 minutes session of interferential electrical stimulation.
Question: Should abdominal transcutaneous electrical stimulation vs sham therapy be used for functional constipation?
Bibliography: Clarke 2009

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abdominal transcutaneous electrical stimulation**	**Sham therapy**	**Relative (95% CI)**	**Absolute**		
Treatment success - not reported												
Withdrawals due to Adverse Events at study end – not reported												

Defecation frequency per week – not reported												
Quality of life measured with PedsQL – not adequately reported												
1												

3. Additional effect: abdominal transcutaneous electrical stimulation + pelvic floor muscle exercises (PFME) vs PFME (N=2)

Notes: In Lady-Seyedian 2020 patients continued PFME for 6 months, Sharifi-Rad 2018 only for 5 weeks and patients were followed up till 6 months. Sharifi-Rad used sham therapy + PFME as control.

Question: Should abdominal transcutaneous electrical stimulation as addition to pelvic floor muscle exercises vs pelvic floor muscle exercises only be used for functional constipation?

Bibliography: Ladi-Seyedian 2020, Sharifi-Rad 2018

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abdominal transcutaneous electrical stimulation + PFME**	**PFME**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 6 months)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	45/62	25/62	RR: 1.75 (1.25 to 2.44) NNT: 3 (2-10)	302 more per 1000 (from 101 more to 581 more per 1000)	Low	
Withdrawals due to Adverse Events at study end (time of measurement: 6 months)												

2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious	Not serious	0/62	1/62	RR: 0.33 (0.01 to 7.97)	11 less per 1000 (from 16 less to 112 more per 1000)	Very low	
Defecation frequency per week (time of measurement: 6 months)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Serious[2]	Not serious	N=62	N=61		MD: 1.85 stools more per week (1.28 stools more per week to 2.43 stools more per week)	Low	
Painful defecation (time of measurement: 6 months)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	2/17	6/17	RR: 0.33 (0.08 to 1.42)	236 less per 1000 (from 311 less to 64 more per 1000)	Very low	
Stool consistency (time of measurement: 6 months)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	3/17	8/17	RR: 0.38 (0.12 to 1.18)	292 less per 1000 (from 414 less to 85 more per 1000)	Very low	
Fecal incontinence (time of measurement: 6 months)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[3]	Not serious	12/62	28/61	RR: 0.43 (0.25 to 0.73)	262 less per 1000 (from 124 less to 344 less per 1000)	Very low	
Adverse events (time of measurement: 6 months)												
2	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[3]	Not serious	0/62	0/62	RR: not estimable	Not estimable	Very low	

[1]Downgraded one level due to unclear allocation concealment and unclear risk of selective reporting

[2]Downgraded one level due to significant imprecision

[3]Downgraded two levels due to serious imprecision

4. Additional effect: abdominal transcutaneous electrical stimulation + standard therapy vs standard therapy (N=1)

Notes: treatment duration of 10 days, follow-up of 3, 6 and 12 months after treatment. Unclear at which time point the reported results are measured. Standard therapy consisted of: laxative diet, probiotics, choleretic drugs, enzymes

Question: Should abdominal transcutaneous electrical stimulation as addition to standard therapy vs standard therapy only be used for functional constipation?

Bibliography: Khan 2020

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abdominal transcutaneous electrical stimulation + standard therapy**	**Standard therapy**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	13/20	10/20	RR: 1.30 (0.75 to 2.24)	150 more per 1000 (from 125 less to 620 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end – not reported												
Defecation frequency per week – not reported												
Painful defecation (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/20	0/20	Not estimable	Not estimable	Very low	
Fecal incontinence (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	4/20	6/20	RR: 0.67 (0.22 to 2.01)	99 less per 1000 (from 234 less to 303 more per 1000)	Very low	

Abdominal pain (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	3/20	5/20	RR: 0.60 (0.17 to 2.18)	100 less per 1000 (from 208 less to 295 more per 1000)	Very low	

[1]Downgraded two levels due to unclear method of allocation concealment, and unclear risk of attrition and selective reporting bias

[2]Downgraded two levels due to very serious imprecision

5. Additional effect: percutaneous tibial nerve stimulation + pelvic floor exercises (PFE) vs sham + PFE (N=1)

Notes: intervention group received percutaneous Tibial Nerve Stimulation (PTNS) with PFE twice daily for 4 weeks. Control group received sham PTNS + PFE twice daily for 4 weeks. PFE was performed using an electromyography biofeedback method, in which an electrode is inserted through the anus.[1] 20-40 hours of progressive resistance training. These hours would be best spread over 4 weeks, with 15 minutes of exercises twice per day.

Question: Should tibial nerve stimulation as an addition to pelvic floor exercises vs pelvic floor exercises be used for functional constipation?

Bibliography: Yu 2023

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tibial nerve stimulation + PFE	PFE	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Very serious[2]	Not serious	26/42	15/42	RR: 1.73 (1.08 to 2.77) NNT: 4 (2 to 35)	261 more per 1000 (from 29 to 632 more per 1000)	Low	
Withdrawals due to Adverse Events at study end (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Very serious[2]	Not serious	3/42	3/42	RR: 1.00 (0.21 to 4.67)	0 more per 1000 (from 56 less to 262 more per 1000)	Low	

Defecation frequency - changes in SBM* per week from baseline (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Serious[3]	Not serious	N=42	N=42		MD: 1.82 higher (from 0.82 higher to 2.82 higher)	Moderate	
Painful or hard defecation – dichotomous: number of children with painful or hard defecation (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Very serious[2]	Not serious	9/42	18/42	RR: 0.50 (0.25 to 0.98)	214 less per 1000 (from 9 less to 321 less per 1000)	low	
Fecal incontinence - dichotomous: number of children with encopresis (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Serious[3]	Not serious	6/42	19/42	0.32 (0.14 to 0.71)	308 less per 1000 (from 131 less to 389 less per 1000)	Moderate	
Serious adverse events (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Very serious[2]	Not serious	0/42	0/42	Not estimable	Not estimable	Very low	
Adverse events (time of measurement: 16 weeks)												
1	Randomised controlled trial	Not serious	Not serious	Not serious	Very serious[2]	Not serious	3/42	4/42	RR: 0.75 (0.18 to 3.15)	24 less per 1000 (from 78 less to 205 more per 1000)	Very low	

[1]Very different way of pelvic floor muscle exercises from how pelvic floor muscle exercises as described in the rest of the literature.

[2]Downgraded two levels due to very serious imprecision

[3]Downgraded one level due to significant imprecision

*SBM: spontaneous bowel movements

Cow's milk free diet

1. Cow's milk free diet vs cow's milk diet (N=2)

Question: Should cow's milk free diet vs cow's milk diet be used for treatment of functional constipation?

Bibliography: Dehghani 2012, Iacono 1998

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cow's milk free diet	Cow's milk diet	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	56/70	33/70	RR: 1.70 (1.29 to 2.23) NNT: 3 (2 to 7)	330 more per 1000 (137 more to 580 more per 100)	Very low	
Withdrawals due to Adverse Events at study end (time of measurements range: 2 to 4 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	0/102	0/102	Not estimable	Not estimable	Very low	
Defecation frequency per week – dichotomous: Number of patients with 3 or more defecations per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	67/70	50/70	RR: 1.34 (1.15 to 1.57) NNT: 4 (2 to 9)	243 more per 1000 (from 107 more to 407 more per 1000)	Very low	
Stool consistency/painful defecation: number of patients with painful or hard bowel movements (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Not serious	9/70	32/70	RR: 0.28 (0.15 to 0.54) NNT: 3 (3 to 5)	329 less per 1000 (from 210 less to 389 less per 1000)	Low	

Fecal incontinence												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	2/70	15/70	RR: 0.13 (0.03 to 0.56) NNT: 5 (5 to 11)	186 less per 1000 (from 94 less to 208 less per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding, unclear allocation concealment and unclear selective reporting
[2]Downgraded one level due to significant imprecision

2. Additional effect: Cow's milk free diet + laxative vs laxative (N=1)

Question: Should Cow's milk free diet as addition to laxative vs laxative alone be used for treatment of functional constipation?
Notes: Children were treated with the osmotic laxative PEG
Bibliography: Bourkheili 2021

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cow's milk free diet + PEG	PEG	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[1]	Not serious	25/35	4/36	RR: 6.43 (2.49 to 16.58) NNT: 2 (1 to 6)	603 more per 1000 (from 166 more to 1000 more per 1000)	Very low	
Withdrawals due to Adverse Events (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[1]	Not serious	0/35	1/36	RR: 0.34 (0.01 to 8.14)	18 less per 1000 (from 28 less to 198 more per 1000)	Very low	

[1]Downgraded two levels due to lack of blinding, unclear allocation concealment and high risk of selective reporting
[2]Downgraded two levels due to significant imprecision

3. Formula with hydrolyzed protein + prebiotics vs formula with cow milk + prebiotics (N=1)

Notes: included children aged 28– 300 days old (4 weeks – 43 weeks)

Question: Should formula with hydrolyzed protein vs formula with cow milk in addition to prebiotics be used for the treatment of functional constipation

Bibliography: Fabrizio 2022

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrolyzed protein + prebiotics	Cow milk + prebiotics	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Serious[3]	7/42	4/47	RR: 1.96 (0.62 to 6.22)	82 more per 1000 (from 32 less to 444 more per 1000)	Very low	
Defecation frequency per day (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Serious[3]	N=42	N=47		MD: 0.50 higher (from 0.22 higher to 0.78 higher)	Very low	
Stool consistency – continuous: scaled as: hard, 1; formed, 2; mushy, 3; unformed or seedy, 4; watery.												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious	Serious[3]	N=42	N=47		MD: 0.40 higher (from 0.12 higher to 0.68)	Very low	
Adverse events (time of measurement: 2 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Serious[3]	14/42	8/47	RR: 1.96 (0.91 to 4.20)	163 more per 1000 (from 15 less to 545 more per 1000)	Very low	

[1]Downgraded two levels due to unclear selective reporting. No protocol could be found. Requested twice from the corresponding author. No response. Pharma sponsored trial, therefore the study should have been registered and a protocol should be available. Therefore, downgraded twice.
[2]Downgraded twice due to very serious imprecision
[3]Protocol or trial registration number not available. Requested twice from the corresponding author. No response. Pharma sponsored trial, therefore study needs to be registered and a protocol available.

Behavioral therapy

1. Additional effect: behavioral therapy (BT) + PEG vs PEG (N=1)

Notes: Behavioral therapy hypothesis: phobic reactions related to defecation can be reduced and that adequate toileting behavior and appropriate defecation straining can be (re)acquired by teaching parents behavioral procedures and by behavioral play therapy with the child in presence of his or her parents. The intervention period for both conventional therapy (laxatives) and BT consisted of 12 visits during 22 weeks with similar intervals between treatment sessions. Conventional therapy consisted of disimpaction with enemas at start, maintenance PEG and if necessary enema or bisacodyl suppositories.

Question: Should behavioral therapy as addition to PEG vs PEG be used for the treatment of functional constipation

Bibliography: van Dijk 2008

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Behavioral therapy + PEG**	**PEG**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: 22 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	35/67	42/67	RR: 0.83 (0.62 to 1.12)	106 less per 1000 (from 238 less to 75 more per 1000)	Low	
Withdrawals due to Adverse Events (time of measurement: 22 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	0/67	1/67	RR: 0.33 (0.01 to 8.21)	10 less per 1000 (from 15 less to 108 more per 1000)	low	
Defecation frequency per week (time of measurement: 22 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Serious[2]	Not serious	N=67	N=67		MD: 1.80 lower (from 0.72 lower to 2.88 lower)	Moderate	

Fecal incontinence frequency per week (time of measurement: 22 weeks)												
1	Randomised controlled trials	Not serious	Not serious	Not serious	Very serious[1]	Not serious	N=67	N=67		MD: 2.90 higher (from 0.97 higher to 4.83 higher)	Low	

[1]Downgraded two levels due to very serious imprecision

[2]Downgraded one level due to significant imprecision

Cryotherapy

1. Cryotherapy + standard therapy vs abdominal electrical stimulation + standard therapy (N=1)

Notes: treatment duration of 10 days, follow-up of 3, 6 and 12 months after treatment. Unclear at which time point the reported results are measured. Standard therapy consisted of: laxative diet, probiotics, choleretic drugs, enzymes

Question: Should cryotherapy vs abdominal electrical stimulation be used as addition to standard therapy for the treatment of functional constipation

Bibliography: Khan 2020

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cryotherpy + standard therapy**	**Abdominal electrical stimulation + Standard therapy**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	15/20	13/20	RR: 1.15 (0.77 to 1.74)	98 more per 1000 (from 150 less to 481 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end – not reported												
Defecation frequency per week – not reported												
Painful defecation (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/20	0/20	Not estimable	Not estimable	Very low	
Fecal incontinence (time of measurement: unclear)												

1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/20	4/20	RR: 0.50 (0.10 to 2.43)	100 less per 1000 (from 180 less to 286 more per 1000)	Very low	
Abdominal pain (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/20	3/20	RR: 0.67 (0.12 to 3.57)	50 less per 1000 (from 132 less to 386 more per 1000)	Very low	

[1]Downgraded two levels due to unclear method of allocation concealment, and unclear risk of attrition and selective reporting bias

[2]Downgraded two levels due to very serious imprecision

2. Additional effect: cryotherapy + standard therapy vs standard therapy (N=1)

Notes: treatment duration of 10 days, follow-up of 3, 6 and 12 months after treatment. Unclear at which time point the reported results are measured. Standard therapy consisted of: laxative diet, probiotics, choleretic drugs, enzymes

Question: Should cryotherapy ad addition to standard therapy vs standard therapy alone be used for the treatment of functional constipation

Bibliography: Khan 2020

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cryotherpy + standard therapy**	**Standard therapy**	**Relative (95% CI)**	**Absolute**		
Treatment success (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	15/20	10/20	RR: 1.50 (0.90 to 2.49)	250 more per 1000 (from 50 less to 745 more per 100)	Very low	
Withdrawals due to Adverse Events at study end – not reported												

Defecation frequency per week – not reported												
Painful defecation (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/20	0/20	Not estimable	Not estimable	Very low	
Fecal incontinence (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/20	6/20	RR: 0.33 (0.08 to 1.46)	201 less per 1000 (from 276 less to 138 more per 1000)	Very low	
Abdominal pain (time of measurement: unclear)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[3]	Not serious	2/20	5/20	RR: 0.40 (0.09 to 1.83)	150 less per 1000 (from 228 less to 208 more per 1000)	Very low	

[1]Downgraded two levels due to unclear method of allocation concealment, and unclear risk of attrition and selective reporting bias

[2]Downgraded two levels due to very serious imprecision

[2]Downgraded one level due to significant imprecision

Massage

1. Additional effect: abdominal and acupressure point massage + traditional Chinese medicine vs traditional Chinese medicine (N=2)

Question: Should abdominal and acupressure point massage as addition to traditional Chinese medicine vs traditional Chinese medicine alone be used for the treatment of functional constipation

Bibliography: Mao 2015, Xu 2015

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abdominal and acupressure point massage + traditional Chinese medicine	Chinese medicine	Relative (95% CI)	Absolute		
Treatment success (time of measurement: at 2 weeks)												
2	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	20/108	13/108	RR: 1.53 (0.81 to 2.91)	64 more per 1000 (from 23 less to 230 more per 1000)	Very low	
Withdrawals due to Adverse Events at study end – not reported												
Defecation frequency per week – not reported												

[1]Downgraded two levels due to unclear method of randomization and allocation concealment, lack of blinding and unclear risk of all other aspects (studies were translated from Chinese)

[2]Downgraded one level due to significant imprecision

2. Additional effect: foot reflexology massage + toilet/diet/motivation training vs toilet/diet/motivation training (N=1)

Question: Should foot reflexology massage as addition to toilet/diet/motivation training vs toilet/diet/motivation training alone be used for the treatment of functional constipation

Bibliography: Canbulat Sahiner 2017

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	foot reflexology massage + toilet/diet/motivation training	Toilet/diet/motivation training	Relative (95% CI)	Absolute		
Treatment success – not reported												
Withdrawals due to Adverse Events at study end – (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/20	0/20	RR: 5.00 (0.26 to 98.00)	200 more per 1000 (from 37 less to 1000 more per 1000)[3]	Very low	
Defecation frequency per week – Number of patients with more than 2 bowel movements per week (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[4]	Not serious	16/20	19/20	RR: 0.84 (0.66 to 1.07)	152 less per 1000 (from 324 less to 66 more per 1000)	Very low	
Stool consistency - number of patients with normal or soft stools (time of measurement: 4 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[4]	Not serious	15/20	18/20	RR: 0.83 (0.62 to 1.12)	153 less per 1000 (from 342 less to 108 more per 1000)	Very low	

[1]Downgraded two levels due to unclear method of randomization and allocation concealment, lack of blinding and unclear risk of selective reporting

[2]Downgraded two levels due to very serious imprecision

[3]Added a fictional event to the control group in order to calculate absolute number to better interpret the result.

[4] Downgraded one level due to significant imprecision

Physiotherapy

1. Additional effect: pelvic physiotherapy + standard medical care vs standard medical care (N=1)

Notes: Pelvic floor physiotherapy consisted of max 6 sessions in 6 months. Standard medical care consisted of education, demystification, dietary advice, toilet training, keeping track of bladder and bowel diaries, and when needed prescription of PEG. Children from both groups were disimpacted with high dose PEG (1–1.5 g/kg for a maximum of 7 days) if a large fecal mass was present at intake (rectal examination was performed to confirm or exclude FC when only 1 Rome III criterion was met) and the dose of maintenance oral PEG was tailored to the individual patient's needs (0.3 – 0.8 g/kg per day). PEG was prescribed to 52 of 53 children (98.1%).

Question: Should pelvic floor physiotherapy as addition to standard medical care vs standard medical care alone be used for the treatment of functional constipation

Bibliography: Van Engelenburg 2017

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pelvic physiotherapy + standard medical care	Standard medical care	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 6 months)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Not serious	Not serious	24/26	12/27	RR: 2.08 (1.34 to 3.21)	480 more per 1000 (from 151 more to 990 more per 1000)	Moderate	
Withdrawals due to Adverse Events at study end (time of measurement: 6 months)												
1	Randomised controlled trials	Serious[1]	Not serious	Not serious	Very serious[2]	Not serious	0/26	0/27	Not estimable	Not estimable	Very low	
Defecation frequency per week – not adequately reported												
Painful and hard stools – not adequately reported												

Fecal incontinence – not adequately reported												

[1]Downgraded one level due to unclear method of allocation concealment

[2]Downgraded two levels due to significant imprecision

2. Additional effect: abdominal muscle training/breathing exercises/abdominal massage + laxative vs laxative (N=1)

Notes: Physiotherapy sessions consisted of isometric training of the abdominal muscles, diaphragmatic breathing exercises and abdominal massage (twice weekly sessions). Laxative treatment in both groups consisted of disimpaction with an enema 1-5 days and maintenance treatment with magnesiumhydroxide.

Question: Should abdominal muscle training/breathing exercises/abdominal massage as addition to laxatives vs laxatives alone be used for the treatment of functional constipation

Bibliography: Silva 2013

GRADE

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**abdominal muscle training/breathing exercises/abdominal massage + laxative**	**Laxative**	**Relative (95% CI)**	**Absolute**		
Treatment success – not reported												
Withdrawals due to Adverse Events at study end (time of measurement: 6 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[2]	Not serious	2/36	8/36	RR: 0.25 (0.06 to 1.10)	167 less per 1000 (from 209 less to 22 more per 1000)	Very low	
Defecation frequency – days per week with defecation (time of measurement: 6 weeks)												

1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[3]	Not serious	N=36	N=36		MD: 1.20 higher (from 0.25 lower to 2.15 higher)	Very low	

[1]Downgraded two levels due to unclear method of randomization and allocation concealment, and unclear risk of selective reporting
[2]Downgraded two levels due to very serious imprecision
[3]Downgraded one level due to significant imprecision

3. Manual therapy vs laxative (N=1)

Notes: Manual physical therapy (MPT) consisted of nine sessions of MPT with a 45-min initial session and 30 min for the rest of sessions distributed weekly during the first and second months and biweekly in the third month. MPT was the same throughout the sessions for all the participants. It was designed and performed by a physiotherapist with 20 years experience in manual physiotherapy, helped by a clinical assistant. The physical treatment was done through direct and indirect articular, vascular, visceral, muscular, and myofascial techniques for the pelvic floor, abdomen (diaphragm, colon, and ileocecal valve, duo- denojejunal flexure), skull, spine (D10–D12), and sacrum, exerting light pressure and vibration, seeking a balance in fascial tensions. it pretended to normalise the neurovegetative, mascular and joint functions.
Control group was kept in the maintenance phase for 2 months until obtaining a regular defecation habit and were treated with PEG followed by a phase of medication withdrawal.
Question: Should manual therapy vs laxative be used for functional constipation?
Bibliography: Blanco Diaz 2020

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual physical therapy	Laxative (PEG)	Relative (95% CI)	Absolute		
Treatment success (time of measurement range:) – not reported												
Withdrawals due to Adverse Events at study end (range:) – not reported												

Defecation frequency per week (time of measurement: 3 months)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N=23	N=21		MD: 1 more per week (from 0.11 more per week to 1.89 more per week)	Very low	
Stool consistency: Modified Bristol Stool Form Scale (scale 1-5) (time of measurement: 1 month)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	N=25	N=21		MD: 0.00 higher (from 0.43 lower to 0.43 higher on the BSFS)	Very low	
Quality of life: PedsQL scale of 0-100, higher scores indicate better QoL (time of measurement: 3 months)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Not serious[2]	Not serious	N=26	N=21		MD: 30.00 higher (from 24.5 higher to 35.5 higher)	Low	

[1]Downgraded due to lack of blinding and high risk of selective reporting

[2]Downgraded one level due to sparse data

Dry cupping

1. Dry cupping vs laxative (N=1)

Notes: laxative used was PEG

Question: Should dry cupping vs laxatives be used for the treatment of functional constipation

Bibliography: Shahamat 2016

GRADE

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dry cupping	Laxative	Relative (95% CI)	Absolute		
Treatment success (time of measurement: 12 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	46/60	50/60	RR: 0.92 (0.77 to 1.10)	67 less per 1000 (from 192 less to 83 more per 100))	Very low	
Withdrawals due to Adverse Events at study end (time of measurement: 12 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Very serious[3]	Not serious	2/60	0/60	RR: 5.00 (0.25 to 102.00)	67 more per 1000 (from 13 less to 1000 more per 1000)[4]	Very low	
Defecation frequency – not adequately reported												
Painful defecation and hard stools - number of patients with painful or hard bowel movements (time of measurement: 12 weeks)												
1	Randomised controlled trials	Very serious[1]	Not serious	Not serious	Serious[2]	Not serious	7/60	10/60	RR: 0.70 (0.29 to 1.72)	50 less per 1000 (from 118 less to 120 more per 1000)	Very low	
Fecal incontinence – not adequately reported												

[1]Downgraded two levels due to unclear method of allocation concealment, and unclear risk of selective reporting and lack of blinding
[2]Downgraded one level due to significant imprecision
[3]Downgraded two levels due to very serious imprecision
[4]Added one fictional event to the control group in Revman in order to calculate absolute numbers to better visualize results

Fluid

1. Increased water intake vs control (N=1)

Notes: measurement of spread was not reported, therefore data could not be analyzed.
Question: Should increased water intake vs standard care be used for the treatment of functional constipation?
Bibliography: Young 1998

Data were not adequately reported. GRADE analyses could not be performed.

2. Increased water intake vs hyperosmolar liquid (N=1)

Notes: measurement of spread was not reported, therefore data could not be analyzed.
Question: Should increased water intake vs hyperosmolar liquid be used for the treatment of functional constipation?
Bibliography: Young 1998

Data were not adequately reported. GRADE analyses could not be performed.

Appendix 7. Secundaire uitkomsten initiële medicamenteuze behandeling

Study	Painful defecation	Stool consistency	Quality of Life	Fecal incontinence	Abdominal pain	School attendance	Tolerability
Enema vs PEG (oral)							
Bekkali 2009	NR	Number of patients with watery stools Enema: 4/41 PEG: 13/39	NR	Frequency per week Enema: 4.9 (5.4) PEG: 5.7 (5.9)	Number of patients with abdominal pain Enema: 23/41 PEG: 17/39	NR	Struggle to administer oral or rectal treatment Enema: 24/38 PEG: 17/31

NR: Not Reported, PEG: polyethylene glycol

Appendix 8. Secundaire uitkomsten onderhoudstherapie medicamenteuze behandeling

Study ID	Painful defecation	Stool consistency	Quality of Life	Fecal incontinence	Abdominal pain	School attendance	Tolerability
PEG vs Placebo							
Modin 2018	NR	NR	NR	NR	NR	NR	NR
Nurko 2008	NR	Reported on a scale from 0-4 (0 = too loose, watery to 4 = very hard). Mean (SD) Dose 0.4: 1.7 (0.6) Dose 0.8: 1.5 (0.7) Placebo: 2.4 (0.9)	NR	Episodes of fecal incontinence per week, mean (SD): Dose 0.4: 1.8 (2.6) Dose 0.8: 3.5 (7.8) Placebo: 1.4 (3.7)	Cramping on a scale of 0-4 (0 = none to 4 = very painful), mean (SD) Dose 0.4: 0.6 (1.0) Dose 0.8: 0.4 (0.7) Placebo: 1.3 (1.3)	NR	NR
Thomson 2007	Not reported pre cross-over	Not reported pre cross-over	NR	Not reported pre cross-over	Not reported pre cross-over	NR	NR
PEG vs Lactulose							
Dheivamani 2021	Number of patients with painful defecation: PEG: 13/50 Lactulose: 24/50	NR	NR	NR	NR	NR	Tolerability to the study medications on a 4-point Likert scale PEG: Poor: 0 Fair: 1 Good: 24 Excellent: 23 Lactulose: Poor: 1 Fair: 5 Good: 19 Excellent: 20
Dupont 2005	NR	NR	NR	NR	Abdominal pain disappearance in	NR	NR

					patients with abdominal pain at baseline. PEG: 9/11 Lactulose: 3/8		
Jarzebicka 2019	Number of patients with painful defecation: PEG: 4/51 Lactulose: 2/51	Stool consistency according to the Bristol Stool Form Scale (BSFS) (scale 1-7). Median (no IQR reported) PEG: 4 Lactulose: 4	NR	NR	NR	NR	NR
Saneian 2012 *Compares PEG vs Lactulose vs Magnesium hydroxide*	NR	NR	NR	NR	Reported as side effect, prevalence of abdominal pain PEG: 2 Lactulose: 14 MgOH: 17	NR	NR
Treepongkaruna 2014	NR	Rating of stool consistency compared to baseline: 0 = harder stool, 1 = no change from baseline, 2 = softer stool. Number of patients with improved stool consistency PEG: 24/43 Lactulose: 27/44	NR	NR	Number of cramps per week. Mean (SD) PEG: 0.14 ± 0.35 Lactulose: 0.43 ± 0.79	NR	Poor compliance if the patient took <70% of the scheduled amount of medication intake in week 4 or <80% over the entire treatment duration PEG: 3/44 Lactulose: 3/44
Uhm 2007	NR	NR	NR	Unclear data	NR	NR	NR

Voskuijl 2004	Number of patients with painful defecation: PEG: 7/50 Lactulose: 21/50	Reported, but only in figure. No data available.	NR	Frequency per week. Mean (SD) PEG: 3.11 (5.41) Lactulose: 2.84 (3.59)	Number of patients with abdominal pain PEG: 16/50 Lactulose: 25/50	NR	Bad palatability according to the patients PEG: 15/50 Lactulose: 5/50
Wang 2007	NR	NR	NR	NR	NR	NR	NR
PEG vs Magnesium hydroxide							
Gomes 2011	NR	Unclear	NR	Unclear	Unclear	NR	Number of patients with bad compliance: unclear. Number of patients with persistent refusal of medication PEG: 0/17 MgOH: 4/21
Loening-Baucke 2006	NR	NR	NR	Fecal incontinence frequency per week, mean (SD). After 12 months. PEG: 1.4 (3.5) MgOH: 0.5 (1.6)	Unclear	NR	Number of patients who continued to refuse the drug after 12 months PEG: 2/39 MgOH: 14/40
Ratanamongkol 2009	Number of patients with episodes of painful defecations. After 4 weeks. PEG: 2/47 MgOH: 11/47	NR	NR	Number of patients with episodes of fecal incontinence. After 4 weeks. PEG: 1/47 MgOH: 1/47	Number of patients reporting abdominal pain. After 4 weeks. PEG: 9/47 MgOH: 14/47	NR	Compliance rate: number of patients who received more than 80% of the medication throughout the study. PEG: 41/47 MgOH: 31/47
PEG vs fibers							
Quitadamo 2012 *Fiber mixture*	Number of patients who reported painful stools	NR	NR	NR	NR	NR	Patient acceptance: number of patients who refused to take the drug PEG: 2/50 Fiber mixture: 14/50

	PEG: 4/50 Fiber: 7/50						
PEG 4000 vs PEG3350 + electrolytes							
Bekkali 2018	NR	NR	NR	NR	NR	NR	Withdrawals due to lack of compliance: PEG 4000: 0 PEG 3350 + E: 1
Savino 2012	Number of days with painful stools. Mean (SD). Unclear if frequency reported per week or per month. PEG 4000: 2.3 (3.8) PEG 3350 + E: 3.2 (4.0)	NR	NR	Number of days with fecal incontinence. Unclear if frequency reported per week or per month. Mean (SD). PEG 4000: 0.5 (1.2) PEG 3350 + E: 0.6 (0.9)	Number of days with abdominal. Unclear if frequency reported per week or per month. Mean (SD) PEG 4000: 2.8 (3.8) PEG 3350 + E: 3.9 (3.7)	NR	Difficulty in administration: PEG 4000 (N=49): 47 no difficulty, 1 mild difficulty, 1 severe difficulty PEG 3350 + E (N=42): 22 no difficulty, 17 mild difficulty, 3 severe difficulty Palatability (5 point scale and ease of administration): PEG 4000 (N=49): 21 good/very good, 27 not good/not bad, 1 bad/very bad PEG 3350 + E (N=42): 1 good/very good, 30 not good/not bad, 11 bad/very bad Compliance (number of patients who took >80% of the described dosage): PEG 4000: 48/49 PEG 3350 + E: 37/42
PEG vs herbal medicine							
Dehghani 2019 *Black strap molasses (BSM) (sugarcane extract)*	Number of patients reporting painful *or* hard stools: PEG: 3/47	Number of patients reporting painful *or* hard stools: PEG: 3/47	NR	NR	NR	NR	NR

	PEG: 3/47 BSM: 10/45	BSM: 10/45					
Esmaeilidooki 2016 *Cassia's fistula emulsion*	Severity of pain during defecation measured on VAS scale (0-100), mean (SD) PEG: 6.54 (11.98) Cassia: 4.74 (8.66)	Stool consistency measured on VAS scale (0-100): PEG: 14.35 (16.8) Cassia: 9.48 (14.6)	NR	Frequency per week, mean (SD) PEG: 1.96 (4.3) Cassia: 1.02 (3.45)	NR	NR	Compliance of the drugs according to VAS pattern, scoring 1 (very good) to 5 (very bad), mean (SD) PEG: 1.88 (1.02) Cassia: 2.33 (1.42) Dropouts due to taste of drug PEG: 2/57 Cassia: 3/57
Imanieh 2022 *R. damascena and brown sugar syrup*	No history of painful *or* hard bowel movements after 4 weeks of treatment PEG: 41/50 R. damascena: 44/50	No history of painful *or* hard bowel movements after 4 weeks of treatment PEG: 41/50 R. damascena: 44/50	NR	Unclear	NR	NR	Feeling of bad taste: PEG: not reported R. damascena: 14/50 Dropouts due to bad taste: PEG: 0/50 R. damascena: 5/50
Nasri 2022 *LaxaPlus Barij®*	Number of patients with existence of pain during defecation PEG: 19/60 LaxaPlus Barij®: 19/60	NR	NR	NR	NR	NR	NR
Nimrouzi 2015 *D. Sohpia seed*	Frequency of painful defecations per week, median (IQR). PEG: 2 (0-3)	Number of hard stools per week, median (IQR). PEG: 0 (0-0)	NR	Frequency per week, median (IQR).	NR	NR	Number of patients who disliked the taste PEG: 5/53 D. Sophia Seed: 17/56

	PEG: 0 (0-3) D. Sophia Seed: 0.5 (0-2)	D. Sophia Seed: : 1 (0-2.75)		D. Sophia Seed: 0 (0-0)			
Saneian 2021 *Goleghand®*	Number of patients with painful defecation PEG: 6/30 Goleghand®: 9/30	NR	NR	NR	NR	NR	NR
Tavassoli 2021 *Viola flower syrup*	Number of painful defecations per week, mean (SD) PEG: 0.40 (0.94) Syrup: 0.25 (1.01)	Number of hard stools per week, mean (SD). PEG: 0.56 (1.15) Syrup: 0.53 (1.13)	NR	Number of fecal soiling per week, mean (SD) PEG: 0.4 (1.25) Syrup: 0.34 (1.27)	NR	NR	Incidence of unpleasant taste PEG: 2/66 Syrup: 1/67
PEG vs Liquid paraffin							
Karami 2009	NAR	NAR	NR	Frequency per month, mean (SD) PEG: 3.9 (0.3) Liquid paraffin: 3.9 (0.3)	NR	NR	NR
Rafati 2011	NR	NR	NR	Number of patients with fecal incontinence at 30^{th} day of treatment PEG: 12/80 Liquid paraffin: 10/78	NAR	NR	NR

PEG vs microenema							
Strisciuglio 2021 *Promelaxin*	NR	Improved stool consistency: patients who experienced an increase, as compared to baseline, of one or more points on the Amsterdam Stool Form Scale (ASFS) or BSFS. PEG: 37/77 Promelaxin: 38/76	Only reported quality of life of parents.	NR	NR	NR	Compliance: the ratio between treatment administered vs. planned, mean (SD). PEG: 84.32% (29.10) Promelaxin: 85.07% (25.23)
Enema as addition to PEG							
Bongers 2009 *Enema: sodium-dioctyl sulfosuccinate and sorbitol*	Number of patients with painful defecation PEG + enema: 11/50 PEG: 17/50	NR	NR	Number of patients with fecal incontinence of less than 1 per week. No data reported, only in figure.	Number of patients with abdominal pain PEG + enema: 17/50 PEG: 22/50	NR	Only patients with PEG + enema answered the question: "I find the application of a rectal enema terrible." Based on a 5-point Likert scale. Very to extremely terrible: 15% of children Quite terrible: 11% No problem at all: 74%
PEG vs prebiotics vs probiotics							
Foroughi 2022 *Prebiotics: psyllium* *Probiotics: L.reuteri, L. rhamnosus, and Bifidobacterium infantis*	Number of painless bowel movements per week, mean (SD) PEG: 6,08 (1,079) PEG + probiotics: 6,36 (0,683)	NR	NR	NR	NR	NR	NR

	Psyllium: 4,50 (1,483) Psyllium + probiotics: 5,19 (1,261)						
PEG vs sodium picosulphate (SP) vs fibers							
Cassetari 2019 *Fibers: green banana biomass (GBB)*	Number of patients with painful defecation PEG: 4 /16 SP: 2/17 GBB: 4/15 GBB+PEG: 3/16 GBB+SP: 1/16	Number of patients with BSFS score higher than 2. PEG: 11/16 SP: 13/17 GBB: 13/15 GBB+PEG: 15/16 GBB+SP: 13/16	NR	Number of patients with > 1 episode of fecal incontinence per week PEG: 4/16 SP: 5/17 GBB: 5/15 GBB+PEG: 2/16 GBB+SP: 2/16	Number of patients with abdominal pain PEG: 2/16 SP: 5/17 GBB: 2/15 GBB+PEG: 2/16 GBB+SP: 4/16	NR	NR
PEG vs dry cupping							
Shahamat 2016	Number of patients with painful or hard bowel movements PEG: 10/60 Cupping: 7/60	Number of patients with painful or hard bowel movements PEG: 10/60 Cupping: 7/60	NR	Number of patients with 1 ≤ episode of fecal incontinence/week PEG: 50/60 Cupping: 55/60	NR	NR	NR
Lactulose vs placebo							
Cao 2018	NR	Difference in stool consistency from baseline measured by BSFS, mean (range) Lactulose: 1.6 (0.9 to 2.3) Placebo: 0.5 (0.2 to 0.9)	NR	NR	Difference in abdominal pain from baseline, based on scale (0=no pain at all, 3=continuous pain), mean (range). Lactulose: -0.2 (-0.5 to -0.1)	NR	NR

					Placebo: -0.1 (-0.3 to -0.1)		
Lactulose vs fibers							
Kokke 2008 *Fiber mixture*	NR	BSFS, mean. No SD reported Lactulose: 4.0 Fiber: 3.6	NR	Number of patients with 1 or more fecal incontinence epidsodes per week. Lactulose: 5/70 Fiber: 9/65	Abdominal pain (0 =not at all,1 = sometimes, 2 =often, and 3=continuous), mean. No SD reported. Lactulose: 1.39 Fiber: 1.49	NR	Number of patients who refused to drink the yoghurt: Lactulose: 11/70 Fiber: 22/65 Taste, rated on a scale of 1–10, median (range). Lactulose: 7 (1-10) Fiber: 8 (1-10)
Ustundag 2010 *Partially hydrolysed guargum (PHG)*	NR	BSFS, mean (SD) Lactulose: 4.3 (0.6) PHG: 3.9 (0.7)	NR	NR	Number of patients with abdominal pain Lactulose: 3/33 PGH: 5/35	NR	NR
Lactulose vs liquid paraffin							
Farahmand 2007	NR	NR	NR	Fecal incontinence frequency per week, in the last 4 weeks, mean (SD). Lactulose: 3 (4.1) Liquid paraffin: 0 (0)	NR	NR	Number of subjects who reported a bad palatability of study medication Lactulose: 8/120 Liquid paraffin: 5/127
Urganci 2005	NR	Stool consistency on a scale of 1-3 (1=hard, 2=firm, 3=loose), mean (SD). During last 4 weeks. Lactulose: 2,21 (0,4) Liquid paraffin: 2,29 (0,2)	NR	NR	NR	NR	NR

Lactulose vs lactitol							
Pitzalis 1995	Number of patients with painful defecation Lactulose: 8/24 Lactitol: 6/27	Number of patients with a stool consistency on a scale of 1-4 (1=hard, 2=normal, 3=soft, 4=liquid). Lactulose (n=23): hard n=3, normal n=15, soft n=1 Lactitol (n=19): hard n=8, normal n=14, soft n=1	NR	Number of patients with fecal incontinence Lactulose: 15/24 Lactitol: 12/27	Number of patients with abdominal pain Lactulose: 15/24 Lactitol: 9/27	NR	*Drug acceptance* (1=bad, 2=mediocre, 3=good, 4=optimal) Lactulose (n=19): bad n=2, mediocre n=4, good n=9, optimal n=4 Lactitol (n=23): bad n=0, mediocre n=5, good n=14, optimal n=4 *Palatabilitly of the drug* (1=bad, 2=mediocre, 3=good, 4=optimal) Lactulose (n=19): bad n=2, mediocre n=3, good n=10, optimal n=4 Lactitol (n=23): bad n=0, mediocre n=4, good n=15, optimal n=4
Lactulose vs probiotics							
Lee 2022 *S. boulardii*	Number of painful defecations per week, mean (SD). Lactulose: 3.38 (1.23) Probiotics: 2.92 (1.04)	BSFS, mean (SD). Lactulose: 3.38 (1.23) Probiotics: 2.92 (1.04)	NR	Frequency per week, mean (SD). Lactulose: 0.53 (1.69) Probiotics: 0.96 (3.63)	NR	NR	NAR
Olgac 2013 *L. reuteri*	Unclear definition	BSFS, mean (SD) Lactulose: 3.5 (0.2) Probiotics: 3.5 (0.2)	KINDL QOL survey (The Improved Quality of Life Survey for Children and Families),	Unclear definition	Unclear definition	NR	NR

			scale of 0-100. Mean, no SD reported. Lactulose: 77 Probiotics: 78				
Lactulose as addition to PEG							
Ala 2015	NR	NR	NR	NR	NR	NR	NR
Magnesiumoxide vs probiotics							
Bu 2007 Compares MgO vs probiotics vs placebo *Probiotics: L. rhamnosus lcr35*	NR	Percentage of hard stools, mean (SD) MgO: 23.5 (7.9) Probiotics: 22.4 (14.7) Placebo: 75.5 (6.1)	NR	Frequency, unclear if per week or per month. MgO: 2.7 (5.1) Probiotics: 2.1 (3.8) Placebo: 2.7 (1.4)	Frequency, unclear if per week or per month. MgO: 4.87 (3.7) Probiotics: 1.9 (1.6) Placebo: 6.7 (3.3)	NR	NR
Kubota 2020 *Compares MgO vs probiotics vs MgO + probiotics Probiotics: L. reuteri*	NR	BSFS, change from baseline to endpoint, least square mean (95% CI) MgO: 1.61 (0.93 – 2.28) Probiotics: 0.62 (-0.07 – 1.32) MgO + probiotics: 0.88 (0.17 - 1.59)	NR	NR	NR	NR	NR
Liquid paraffin vs herbal medicine							
Mozaffarpur 2012 *Cassia fistula emulsion*	Pain severity, reported on VAS score (0-100), mean (SD) Liquid paraffin: 20.1 (19.9)	Stool consistency, reported on VAS score (0-100), 0=soft. Mean (SD) Liquid paraffin: 25.4 (22)	NR	Fecal incontinence frequency per week, mean (SD). Liquid paraffin: 6.4 (11.1) Herbal: 3 (9.1)	NR	NR	Parents were asked to explain the acceptance and tolerance of drugs on scale of 1-7: taking drug, with willingness = 1. Vomiting, if anyway takes it = 7. Mean (SD). Liquid paraffin: 2.4 (1.3)

	Herbal: 4.8 (8.5)	Herbal: 11.9 (16.8)					Herbal: 2.2 1(1.5)
Liquid paraffin vs synbiotics							
Khodadad 2010 *Multispecies probiotics + fructo-oligosaccharides*	Number of patients with painful defecations Liquid paraffin: 2/29 Synbiotics: 3/31	Number of patients with hard stools Liquid paraffin: 2/29 Synbiotics: 7/31	NR	Frequency per week, mean (SD) Liquid paraffin: 0.24 (1.3) N=29 Synbiotics: 0.06 (0.25) N=31	Number of patients with abdominal pain Liquid paraffin: 4/29 Synbiotics: 2/31	NR	NR
Lubiprostone vs placebo							
Benninga 2022	Painfulness of spontaneous bowel movements (4-point scale: 1=mild and 4=severe), mean change from baseline (SD). Lubiprostone: -0.81 (1.02) Placebo: -0.65 (1.1)	NR	NR	Frequency per 2 weeks, mean change from baseline (SD) Lubiprostone: 0.04 (0.37) Placebo: 0.07 (0.48)	Abdominal pain (4-point scale with 1=mild and 4=severe), mean change from baseline (SD) Lubiprostone: -0.42 (0.84) Placebo: -0.35 (0.76)	NR	NR
Prucalopride vs placebo							
Mugie 2014	Change from baseline of level of defecation pain (scale 0-5), mean (SD) Prucalopride: -0.6 (1.36)	BSFS, mean change from baseline (SD). Prucalopride: 0.6 (1.41) Placebo: 0.1 (1.17)	PedsQL questionnaire, mean change from baseline (SD). *Patient reported*	Frequency per 2 weeks, mean change from baseline (SD) Prucolopride: 8.7 (36.85) Placebo: 13,9 (64.91)	Level of abdominal pain (Wong–Baker Faces Pain Rating Scale 0-5), mean change from baseline (SD)	NR	NR

	Placebo: -0.4 (0.94)		Prucalopride: 3.9 (13.8) Placebo: 2.7 (12.4) *Parent reported* Prucalopride: 6.5 (13.9) Placebo: 4.1 (14.2)		Prucalopride: -0.2 (0.76) Placebo: -0.3 (0.94)		
Linaclotide vs placebo							
Di Lorenzo 2020	NR	BSFS (1-7), mean change form baseline (SD) Lin: 1.16 (1.51) Placebo: 0.40 (1.51)	NR	Change from baseline in 4-week fecal incontinence daytime per day, mean (SD) Linaclotide: PEG: 0,17 (0,3) (n=10) Placebo: -0,03 (0,08) (n=11)	Abdominal pain on scale of 0-4 0=none, 4=a lot. Mean change from baseline (SD) Lin: -0.12 (0.88) Placebo: -0.43 (0.85)	NR	NR
Di Lorenzo 2024	NR	BSFS (1-7), mean (SD) Lin: 3.5 (0.94) Placebo: 3.08 (0.85)	NR	Number of patients with fecal incontinence at the end of treatment (12 weeks) Lin: 28/136 Placebo: 26/136	Abdominal pain on scale of 0-4 0=none, 4=a lot. Mean change from baseline (SD) Lin: -0.53 (0.76) Placebo: -0.34 (0.73)	NR	NR
Domperidone as addition to PEG							
Dehghani 2014	Number of patients with history of hard and painful	Number of patients with history of hard	NR	Number of patients with ≥1 dirty underwear per week	NR	NR	NR

	bowel movements PEG + domperidone: 10/52 PEG + placebo: 11/53	and painful bowel movements PEG + domperidone: 10/52 PEG + placebo: 11/53		PEG + domperidone: 10/52 PEG + placebo: 7/53			

NR: not reported, BSFS: Bristol Stool Form Scale scores (7-point scale, 1 = separate hard lumps to 7 = watery stool), NAR: not adequately reported, PedsQL: Pediatric Quality of Life

Appendix 9. Secundaire uitkomsten niet-medicamenteuze behandeling

Study	Painful defecation	Stool consistency	Quality of Life	Fecal incontinence	Abdominal pain	School attendance	Tolerability
Probiotics vs placebo							
Lojanatorn 2023	Painful defecation per week, median (IQR) Probiotics: 0,5 (0-2) Placebo: 0 (0-2)	Bristol stool grade, on scale of 1-7 (1= very hard, 7=very loose), mean (SD) Probiotics: 2,8 (1,2) Placebo: 2,8 (1,2)	NR	NR	NR	NR	NR
Tabbers 2011	Number of children with pain during defecation Probiotics: 36/79 Placebo: 31/80	Mean stool consistency, based on Bristol stool scale (1-7), mean. No SD reported. Probiotics: 3.3 Placebo: 3.5	NR	Proportion of patients with episodes of fecal incontinence. Probiotics: 27/79 Placebo: 36/80	Number of children with abdominal pain Probiotics: 43/79 Placebo: 40/80	NR	NR
Tjokronegoro 2020	Number of patients with painful defecation Probiotics: 8/39 Placebo: 19/39	Number of patients with normal stool consistency. Probiotics: 27/39 Placebo: 17/39	NR	Number of patients who had stool incontinence Probiotics: 2/39 Placebo: 7/39	NR	NR	Compliance was checked by interview and counting the sachets returned by the parents. Not reported what was considered as good compliance. Not reported per group: “63% had good compliance”
Zaja 2021	NR	Number of patients with normal stool consistency.	NR	NR	NR	NR	NR

		Probiotics: 12/15 Placebo: 14/16					
Bu 2007 *L. rhamnosus lcr35 vs Placebo vs MgO*	NR	Percentage of hard stools, mean (SD) Probiotics: 22.4 (14.7) Placebo: 75.5 (6.1) MgO: 23.5 (7.9)	NR	Frequency, unclear if per week or for whole 4 weeks of treatment. Probiotics: 2.1 (3.8) Placebo: 2.7 (1.4) MgO: 2.7 (5.1)	Frequency, unclear if per week or for whole 4 weeks of treatment. Probiotics: 1.9 (1.6) Placebo: 6.7 (3.3) MgO: 4.87 (3.7)	NR	NR
Wojtyniak 2017	Pain during defecation per week, median (IQR) Probiotics: 0.0 (0.0-1.0) Placebo: 0.0 (0.0-1.0)	Bristol Stool Form Scale (1-7), median (IQR). Probiotics: 3.5 (2.8, 4.0) Placebo: 3.7 (3.0, 4.0)	NR	Fecal soiling per week, median (IQR) Probiotics: 0.0 (0.0, 0.0) Placebo: 0.0 (0.0, 0.0)	Abdominal pain, median (IQR) Probiotics: 0.0 (0.0, 0.0) Placebo: 0.0 (0.0, 0.0)	NR	NR
Gan 2022	NR	Bristol Stool Score (3-5 = normal stools) For each child, the ratio of the number of occurrences to the total number of stools (%) was calculated. Probiotics: 80% normal stools Placebo: 61 normal stools	NR	NR	NR	NR	NR
Coccorullo 2010	NR	Reported hard stools Probiotics: 18.2% Placebo: NR	NR	NR	NR	NR	Excellence compliance: no violation of the protocol for the

							study product intake Probiotics: 94.6% Placebo: 86.9%
Probiotics vs laxatives							
Kubota 2020 *L. reuteri vs MgO*	NR	BSFS, change from baseline to endpoint, least square mean (95% CI) Probiotics: 0.62 (-0.07 – 1.32) MgO: 1.61 (0.93 – 2.28)	NR	NR	NR	NR	NR
Lee 2022 *S. boulardii vs Lactulose*	Number of painful defecations per week, mean (SD). Probiotics: 0.68 (0.75) Lactulose: 0.48 (0.5) Probiotics + Lactulose: 0.64 (0.97)	BSFS (1-7). Mean (SD). Probiotics: 2.92 (1.04) Lactulose: 3.38 (1.23) Probiotics + lactulose: 3.54 (1.32)	NR	Frequency per week, mean (SD) Probiotics: 0.96 (3.63) Lactulose: 0.53 (1.69) Probiotics + Lactulose: 0.56 (1.66)	NR	NR	Number of patients with drug changes due to poor treatment outcome, poor compliance, and/or other side effects. Unclear what the exact reasons were for drug change per patient. S. boulardii: n=23 Lactulose: n=3 Combination: n=7
Olgaç 2013 *L. reuteri vs lactulose*	Reduction rate in % (no further information) Probiotics: 80% Lactulose: 68%	BSFS (1-7). Mean (SD). Probiotics: 3.5 (0.2) Lactulose: 3.5 (0.2)	KIND QOL survey (0-100), high scores = high QoL. Mean, but no SD reported. Probiotics: 77 Lactulose: 78	Reduction rate in % (no further information) Probiotics: 8% Lactulose: 14%	Reduction rate in % (no further information) Probiotics: 64% Lactulose: 29%	NR	NR

Probiotics as addition to laxatives							
Abediny 2016 *Multispecies and PEG*	NR	Number of patients with hard stools Probiotics+PEG: 5/45 PEG: 8/45	NR	NR	Number of patients with abdominal pain Probiotics+PEG: 7/45 PEG: 16/45	NR	NR
Banaszkiewicz 2005 *Lactobacillus GG and lactulose*	NR	NR	NR	Frequency per week, mean (SD) Probiotics+lactulose : 0.8 (1.8) Probiotics+placebo: 0.3 (0.9)	NR	NR	NR
Jadrešin 2018 *L. reuteri and lactulose*	NR	NR	NR	NR	Abdominal pain on scale (scale not reported), median (IQR) Probiotics + lactulose: 0.2 (0-2) Lactulose: 0.5 (0-2)	NR	Compliance discussed with withdrawals but no reasons given. Probiotics + lactulose: 2/18 Lactulose: 4/15
Foroughi 2022 *Laxative: PEG* *Prebiotics: psyllium* *Probiotics: L.reuteri, L. rhamnosus, and Bifidobacterium infantis*	Painless bowel movements per week, mean (SD) Probiotics+PEG: 6.36 (0.683) PEG: 6.08 (1.079) PEG + probiotics: 6,36 (0,683) Psyllium: 4,50 (1,483) Psyllium + probiotics: 5,19 (1,261)	NR	NR	NR	NR	NR	NR

Kubota 2020 *Multispecies and Magnesiumoxide*	NR	Change from baseline to endpoint, least square mean (95% CI) Probiotics+MgO: 0.88 (0.17, 1.59) MgO: 1.61 (0.93 – 2.28)	NR	NR	NR	NR	NR
Russo 2017 *Multispecies and PEG*	NR	BSFS (1-7), mean (SD) Probiotics+PEG: 4.2 (0.5) PEG: 4.2 (0.5)	NR	Number of patients with fecal incontinence Probiotics + PEG: 2/25 PEG: 1/25	Number of patients with abdominal pain Probiotics +PEG: 1/25 PEG: 2/25	NR	Refused due to bad taste: Probiotic+PEG: 1/25 PEG: 1/25
Sadeghzadeh 2014 *Multi species and lactulose*	NR	Hard, normal, soft stools (1-3), mean (SD) Probiotics+lactulose: 0.88 (0.45) Lactulose+placebo: 0.63 (0.50)	NR	Number of patients with fecal incontinence. Only looked at patients who had fecal incontinence before intervention. Probiotics + lactulose: 4/15 Lactulose+placebo: 7/9	Number of patients with abdominal pain. Only looked at patients who had abdominal pain before intervention. Probiotics + lactulose: 7/16 Lactulose+placebo: 12/14	NR	NR
Wegner 2018 *L. reuteri + PEG*	Number of patients with painful defecation Probiotics+PEG: 13/65 PEG: 8/64	Number of patients passing hard stools Probiotics+PEG: 7/65 PEG: 3/64	NR	Number of patients with presence of fecal incontinence: Probiotics + PEG: 17/59 PEG: 11/61	Number of patients with abdominal pain Probiotics + PEG: 19/65 PEG: 25/64	NR	Withdrawals due to lack of compliance: Probiotics + PEG: 5/65 PEG: 1/64
Probiotics as addition to goat yoghurt							

Guerra 2011 *B. longum*	Defecation pain: No numbers reported	Number of patients with Bristol stool scale < 4 (based on 5 point scale) No numbers reported		NR	Abdominal pain: No numbers reported	NR	NR
Formula with intact protein + probiotic + PEG vs Formula with hydrolyzed whey + PEG							
Sevilla 2022	Number of subjects indicating to suffer from painful defecation Formula 1: 6/47 Formula 2: 6/48	Number of subjects who reported to have a hard stool on one or more occasions throughout the intervention: Formula 1: 10/47 Formula 2: 14/48	NR	Number of subjects indicating to suffer from fecal incontinence (defined as passing stool whilst asleep): Formula 1: 10/47 Formula 2: 14/48	NR	NR	NR
Herbal medicine vs laxative							
Dehghani 2019 *Black strap molasses (sugarcane extract) vs PEG*	Number of patients with hard or painful stools BSM: 10/45 PEG: 3/47	Number of patients with hard or painful stools BSM: 10/45 PEG: 3/47	NR	NR	NR	NR	NR
Esmaeilidooki 2016 *Cassia's fistula emulsion vs PEG*	Severity of pain measured on VAS score (0-100), mean (SD) Cassia's fistula: 4,74 (8,66) PEG: 6,54 (11,98)	Measured on Visual Analog Scale (0-100). 0 = softer. Cassia's fistula: 9,48 (14,6) PEG: 14,35 (16,8)	NR	Frequency per week, mean (SD) Cassia's fistula emulsion: 1,02 (3,45) PEG: 1,96 (4,3)	NR	NR	Compliance of the drugs according to VAS pattern, scoring 1 (very good) to 5 (very bad), mean (SD) Cassia's fistula: 2,33 (1,42) PEG: 1,88 (1,02) Dropouts due to taste of drug

							Cassia's fistula: 3/57 PEG: 2/57
Imanieh 2022 *R. damascena and brown sugar syrup vs PEG*	No history of painful or hard bowel movements after 4 weeks of treatment R damascena: 44/50 PEG: 41/50	No history of painful or hard bowel movements after 4 weeks of treatment R damascena: 44/50 PEG: 41/50	NR	Unclear data	NR	NR	Number of patients who dropped out due to bad taste R. damascena: 5/50 PEG: 0/50 Feeling of bad taste: R. damascene: 14/50 PEG: NR
Mozaffarpur 2012 *Cassia fistula emulsion vs Liquid Paraffin*	Pain severity, reported on VAS score (0-100), mean (SD) Cassia fistula: 4.8 (8.5) Liquid paraffin: 20.1 (19.9)	Stool consistency, reported on VAS score (0-100), 0=soft. Mean (SD) Cassia's fistula: 11.9 (16.8) Liquid Paraffin: 25.4 (22)	NR	Frequency per week, mean (SD) Cassia's fistula: 4.8 (8.5) Liquid paraffin: 20.1 (19.9)	NR	NR	NR
Nasri 2022 *LaxaPlus Barij® vs PEG*	Number of patients with existence of pain during defecation LaxaPlus Barij®: 19/60 PEG: 19/60	NR	NR	NR	NR	NR	NR
Nimrouzi 2015 *D. Sohpia seed vs PEG*	Frequency of painful defecations per week, median (IQR)	Frequency of hard stool per week, median (IQR) D. Sophia seed: 1 (0-	NR	Frequency per week, median (IQR) D. Sophia seed: 0 (0-0) PEG: 0 (0-0)	NR	NR	Number of patients who disliked the taste.

	D. Sophia seed: 0,5 (0-2) PEG: 0 (0-3)	2.75) PEG: 2 (0-3)					D. Sohpia seed: 17/56 PEG: 5/53
Saneian 2021 *Goleghand® vs PEG*	Number of patients with painful defecation Goleghand®: 9/30 PEG: 6/30	NR	NR	NR	NR	NR	NR
Tavassoli 2021 *Viola flower syrup vs PEG*	Number of painful defecations per week, mean (SD) VFS: 0,25 (1,01) PEG: 0,40 (0,94)	Number of hard stools per week, mean (SD) VFS: 0.53 (1.13) PEG: 0.56 (1.15)	NR	Number of fecal soiling per week, mean (SD) Viola flower syrup: 0,34 (1,27) PEG: 0,4 (1,25)	NR	NR	Incidence of unpleasant taste VFS: 1/67 PEG: 2/66
Herbal medicine vs placebo							
Cai 2018 *Xiao'er Biantong granules*	NR	Dry stool (1 and 2 of Bristol Stool Scale). Disappearance rate of dry stool, n(%). XBG: 236/360 Placebo: 11/120	NR	Disappearance rate of fecal incontinence, n(%). XBG: 3/5 Placebo: 0/3	NR	NR	NR
Manual physical therapy vs laxative							
Blanco Diaz 2020	NR	Bristol Stool form Scale (modified 1-5 scale). Median (IQR) Manual physical therapy: 4 (3-4) PEG: 4 (3-4)	PedsQL questionnaire, scale of 0-100, higher scores indicate better QoL. Unclear if parent or child filled in questionnaire. Median (IQR). Manual physical	NR	NR	NR	NR

			therapy: 89 (82 – 94) PEG: 59 (50 -63)				
Cow's milk free diet vs cow's milk diet							
Iacono 1998	Categorized: (1) mushy/liquid, (2) soft, (3) hard and difficulty and pain on passing stools. Number of patients per group. Not reported pre cross-over. CMFD: Group 1: n=2 Group 2: n=42 Group 3: n=21 CMD: Group 1: n=0 Group 2: n=0 Group 3: n=65	Categorized: (1) mushy/liquid, (2) soft, (3) hard and difficulty and pain on passing stools. Number of patients per group. Not reported pre cross-over. CMFD: Group 1: n=2 Group 2: n=42 Group 3: n=21 CMD: Group 1: n=0 Group 2: n=0 Group 3: n=65	NR	NR	NR	NR	NR
Dehghani 2012	Number of patients with painful or hard bowel movements CMFD: 9/70 CMD: 32/70	Number of patients with painful or hard bowel movements CMFD: 9/70 CMD: 32/70	NR	Number of patients with ≥ 1 episode/week CMFD: 2/70 CMD: 15/70	NR	NR	NR
Cow's milk free diet + PEG vs PEG							
Bourkheili 2021	Unclear data	Unclear data	NR	Unclear data	NR	NR	NR
Formula with partially hydrolyzed cow's milk protein + prebiotics mix vs Formula based on cow's milk + prebiotics mix							
Fabrizio 2022	Participants who ever cried, fussed or	Parent-reported stool consistency was scaled as, mean	NR	NR	NR	NR	NR

	appeared in pain while having or attempting to have a bowel movement No numbers reported	(SE): hard, 1; formed, 2; mushy, 3; unformed or seedy, 4; watery. Formula 1: 3.4 (0.1) Formula 2: 3.0 (0.1)					
Fluid intake							
Young 1998 *Increased water intake vs hyperosmolar liquid vs control*	NR	Stool consistency on Stool Consistency Continuum (1= watery, 7/8 = hard), mean (no SD reported) Increased water: 5.79 Hyperosmolar: 6.3 Control: NR	NR	NR	NR	NR	NR
Parasacral transcutaneous electrical nerve stimulation (PTENS) vs sham therapy							
De Abreu 2021	Number of patients with pain/straining during defecation after treatment PTENS: 0/20 Sham: 0/20	Number of patients with stool type 1 or 2 on Bristol Stool Scale (hard) after treatment PTENS: 5/20 Sham: 10/20	NR	Number of patients with episode of fecal incontinence after treatment PTENS: 2/20 Sham: 4/20	NR	NR	NR
Abdominal transcutaneous electrical stimulation (TES) vs sham therapy							
Clarke 2009	NR	NR	Parental and child perceived PedsQL (0-100), mean. no SD reported <u>TES</u> Parental: 70.1	NR	NR	NR	NR

			Child: 81.1 Sham Parental: 70.2 Child: 78.1				
Abdominal transcutaneous electrical stimulation (TES) as addition to pelvic floor muscle exercise (PFME)							
Ladi-Seyedian 2020	Number of patients with painful defecation: TES + PFME: 2/17 PFME: 6/17	Number of patients with abnormal stool form: TES + PFME: 3/17 PFME: 8/17	NR	Number of patients with fecal soiling TES + PFME: 0/17 PFME: 1/17	NR	NR	NR
Sharifi-Rad 2018	Number of patients with painful or hard bowel movements TES + PFME: 6/45 PFME: 14/44	Number of patients with painful or hard bowel movements TES + PFME: 6/45 PFME: 14/44	Constipation-related QOL score, median (IQR). No scale reported. TES + PFME: 64 (5) PFME: 62 (6)	Number of patients with ≥1 episodes per week TES + PFME: 12/45 PFME: 27/44	NR	NR	NR
Abdominal transcutaneous electrical stimulation (TES) and cryotherapy and standard therapy (ST)							
Khan 2020	Number of patients with painful defecation: TES + ST: 0/20 Cryotherapy + ST: 0/20 ST: 0/20	NR	NR	Number of patients with fecal incontinence: TES + ST: 4/20 Cryotherapy + ST: 2/20 ST: 6/20	Number of patients with abdominal pain: TES + ST: 4/20 Cryotherapy + ST: 2/20 ST: 5/20	NR	NR
Percutaneous tibial nerve stimulation (PTNS) as addition to Pelvic Floor Exercises (PFE)							
Yu 2023	Number of patients with painful or hard bowel movements PTNS + PFE:	Number of patients with painful or hard bowel movements PTNS + PFE: 33/42 PFE: 24/42	NR	Number of patients with encopresis PTNS + PFE: 36/42 PFE: 23/42	NR	NR	Number of patients withdrawn due to low compliance PTNS + PFE: 2/42 PFE: 2/42

	33/42 PFE: 24/42						
Self-monitoring and reward system to increase fiber intake vs standard dietary advice							
Sullivan 2012	NR	NR	NR	NR	NR	NR	NR
Additional effect of behavioral therapy to laxatives							
Van Dijk 2008	NR	NR	NR	Number of episodes per week, mean (95% CI) Behavioral + PEG: 8.6 (4.0–18.3) PEG: 6.4 (3.5–11.7)	NR	NR	NR
Biofeedback vs no biofeedback							
Castilla 2021 (abstract only)	NR	NR	NR	NR	NR	NR	NR
Additional effect of biofeedback to laxatives							
Loening-Baucke 1990 *Vs magnesiumhydroxide*	NR	NR	NR	Frequency per week, mean (SD) Biofeedback + MgOH: 1 (1) MgOH: 3 (6)	NR	NR	NR
Sunic-Omejc 2002 *vs Lactulose*	NR	NR	NR	NR	NR	NR	NR
Van der Plas 1996 *vs lactitol*	NR	NR	NR	NR	NR	NR	NR
Additonal effect of biofeedback at home to biofeedback in laboratory							
Croffie 2005	NR	NR	NR	Number of soiling episodes per week, mean. Unclear if SD or SE. Biofeedback home + laboratory: 0.08 (0.08) Laboratory feedback: 0.08 (0.08)	NR	NR	NR
Fiber vs placebo							

Chmielewska 2011 *Glucomannan*	Episodes per week, median (IQR). Fiber: 0 (0-1) Placebo: 0 (0)	BSFS (1-7), mean (SD) Fiber: 3.1 (1.1) Placebo: 3.2 (1.0)	NR	NR	Episodes per week, median (IQR) Fiber: 0 (0-2) Placebo: 0 (0-1)	NR	1 patient discontinued from fiber group due to "bad taste"
Loening-Bauke 2004 *Glucomannan*	NR	NR pre cross-over	NR	NR pre cross-over	NR pre cross-over	NR	NR
Weber 2014 *Fiber mixture*	-	BSFS (1-7) subgrouped as non-hardened (4-7) Fiber: 12/27 Placebo: 4/30	NR	NR	NR	NR	NR
Fiber vs laxative							
Kokke 2008 *Fiber mixture vs lactulose*	NR	BSFS (1-7), mean, SD not reported. Fiber: 3.6 Lactulose: 4.0	NR	Number of patients with 1 or more fecal incontinence episodes per week. Fiber: 9/70 Lactulose: 5/70	NR	NR	NR
Üstündağ 2010 *Partially hydrolysed guargum vs lactulose*	NR	NR	NR	NR	Number of patients with abdominal pain Fiber: 5/35 Lactulose: 3/33	NR	NR
Cassetari 2019 *Green banana biomass vs PEG and vs Sodium Picosulfate*	Number of patients who reported painful stools GBB: 4/15 PEG: 4/16 SP: 2/17	Number of patients with BSFS higher than 1 or 2 (hard stools) GBB: 13/15 PEG: 11/16 SP: 13/17	NR	NR	Number of patients with abdominal pain GBB: 5/15 PEG: 2/16 SP: 5/17	NR	NR
Quitadamo 2012 *Fiber mixture vs PEG*	Number of children with painful defecation	BSFS (1-7), mean (SD) Fiber: 3.5 (0.2) PEG: 3.7 (1.0)		Frequency of fecal incontinence per week, mean (SD) Fiber: 0.3 (1.1) PEG: 0.2 (1.3)	Number of patients with abdominal pain Fiber: 5/36 PEG: 6/47	NR	NR

	Fiber: 7/50 PEG: 4/50						
Prebiotics vs placebo							
Da Silva Souza *Fructo-oligosaccharides*	% of bowel movements, mean (SD) Prebiotics: 14.68 ± 29 Placebo: 28.39 (43.82)	as % of BMs with soft stool consistency, mean (SD) Prebiotics: Placebo: 55.38 (36.32)	NR	NR	NR	NR	All participants who completed the 4-week intervention (n = 36) consumed more than 80% of the delivered amount of FOS or placebo.
Formula with prebiotics and hydrolyzed whey protein vs standard formula							
Savino 2005 *Galactooligosaccharides and fructo-oligosaccharides*	NR	Number of patients with hard, formed or watery/runny stools New formula: 38/55 hard, 14/55 formed, 3/55 runny Standard formula: 23/40 hard, 13/40 formed, 4/40 runny	NR	NR	NR	NR	NR
Bongers 2007 *Galactooligosaccharides and fructo-oligosaccharides*	Number of patients who had no painful defecation New formula: 7/20 Standard formula: 5/15	Number of patients with improvement of hard to soft stools New formula: 9/10 Standard formula: 5/10	NR	NR	NR	NR	NR
Synbiotics vs placebo							
Baştürk 2017	Number of patients with painful defecation	NAR	NR	NAR	Number of patients with abdominal pain Synbiotics: 4/77		

	Synbiotics: 16/77 Placebo: 27/78				Placebo: 41/78		
Synbiotics and laxative							
Khodadad 2010 *Multispecies probiotics + fructo-oligosaccharides* *Laxative: liquid paraffin*	Number of patients with painful defecations Synbiotics: 3/31 Liquid paraffin: 2/29 Synbiotics+Liquid paraffin: 4/37	Number of patients with hard stools Synbiotics: 7/31 Liquid paraffin: 2/29 Synbiotics+Liquid paraffin: 4/37	NR	Frequency per week, mean (SD) Synbiotics: 0.06 (0.25) Liquid paraffin: 0.24 (1.3) Synbiotics+Liquid paraffin: 0 (0)	Number of patients with abdominal pain Synbiotics: 2/31 Liquid paraffin: 4/29 Synbiotics+Liquid paraffin: 5/37	NR	NR
Abdominal and acupressure point massage as addition to traditional Chinese medicine							
Mao 2015	NR	NR	NR	NR	NR	NR	NR
Xu 2015	NR	NR	NR	NR	NR	NR	NR
Foot reflexology massage as addition to toilet/diet/motivation training							
Canbulat Sahiner 2017	NR	Number of patients with normal or soft stools Foot reflexology massage + standard therapy: 15/20 Standard therapy: 18/20	NR	NR	NR	NR	Compliance was assessed for toilet/diet/motivation training per week as yes/no for compliance. No difference for toilet training and compliance to motivation. Control group followed the diet more closely and the difference was statistically significant from the second week.
Pelvic physiotherapy as addition to standard medical care							

Van Engelenburg 2017 *Laxative: PEG*	Painful/hard stools: number of patients with improvement from baseline Physio: 15/15 Standard care: 10/17	Painful/hard stools: number of patients with improvement from baseline Physio: 15/15 Standard care: 10/17	NR	Fecal incontinence: number of patients with improvement from baseline Physio: 13/15 Standard care: 10/15	NR	NR	NR
Abdominal muscle training/breathing exercises/abdominal massage as addition to laxatives							
Silva 2013 *Laxative: Magnesium Hydroxide (MgO)*	NR	NR	NR	NR	NR	NR	NR
Dry cupping vs laxative							
Shahamat 2016 *PEG*	Number of patients with painful or hard bowel movements Dry cupping: 7/60 PEG: 10/60	Number of patients with painful or hard bowel movements Dry cupping: 7/60 PEG: 10/60	NR	Not adequately reported	NR	NR	NR

NR: not reported, NAR: not adequately reported

Appendix 10. Bijwerkingen studies initiële medicamenteuze behandeling

Study	Intervention	Control
Enema vs PEG (oral)		
Bekkali 2009	Only reported abdominal pain soon after treatment: 31/38	Only reported abdominal pain soon after treatment: 15/31

Appendix 11. Bijwerkingen studies onderhoudstherapie medicamenteuze behandeling

Study	Intervention	Control
PEG vs Placebo		
Modin 2018	SAE None AE (only reported for gastrointestinal symptoms) The reported adverse events possibly related to study drug were: abdominal pain N=6 and bloating N=1 Total number of children with AE related to gastrointestinal tract: 28%	SAE None AE (only reported for gastrointestinal symptoms) The reported adverse events possibly related to study drug were: abdominal pain N=22 and bloating N=0 Total number of children with AE related to gastrointestinal tract: 69%
Nurko 2008	SAE Dose 0.2 g/kg: hospitalization due to impaction N=2 AE Dose 0.4 g/kg: number of children with an AE = 16/27 (59.3%) Dose 0.8 g/kg: number of children with an AE = 17/26 (65.4%) Type of AE not reported per patient	SAE Hospitalization due to exacerbation of bipolar disorder and depression N=1 AE Number of children with an AE = 14/24 (58.3%) Type of AE not reported per patient
Thomson 2007	NR pre cross-over. During complete trial: 31/49 (63.3%)	NR pre cross-over During complete trial: 28/49 (57.1%)
PEG vs Lactulose		
Dheivamani 2021	SAE NR AE Number of children with an AE: 1/50 Fever N=1	SAE NR AE None
Dupont 2005	SAE None AE Number of children with an AE: 2/51 Diarrhea N=2	SAE None AE Number of children with an AE: 3/45 Diarrhea N=2, anorexia N=1

Jarzebicka 2019	SAE None AE Number of children with an AE: 27/46 Prevalence of AE's: abdominal pain N=10, Diarrhea N=6, Nausea/vomiting N=1, Bloating/gas N=20, Irritation of the anal area N=2	SAE None AE Number of children with an AE: 38/49 Prevalence of AE's: abdominal pain N=17, Diarrhea N=3, Nausea/vomiting N=1, Bloating/gas N=35, Irritation of the anal area N=9
Saneian 2012 *PEG vs Lactulose vs Magnesium hydroxide (MgOH)*	SAE NR AE Number of children with an AE: NR Number of children with specific AE: Bloated N=2, stomach irritation N=1, abdominal pain N=1	SAE NR AE Number of children with an AE: NR Number of children with specific AE (Lactulose): Nausea and vomiting N=1, Bloated N=17, diarrhea N=1, Stomach irritation N=2, abdominal pain N=14 Number of children with specific AE (MgOH): Bloated N=1, diarrhea N=5, Stomach irritation N=1, abdominal pain N=17
Treepongkaruna 2014	SAE Pneumonia N=1, Road traffic accident N=1 AE Number of children with an AE: 27/44 Anal dilatation N=14, Upper respiratory tract infections N=9, Anal fissure N=9, Faecaloma N=5, Hard faeces N=3, Anal skin tags N=5, Rhinorrhoea N=3, Vomiting N=3	SAE Varicella infection N=1 AE Number of children with an AE: 26/44 Anal dilatation N=10, Upper respiratory tract infections N=9, Anal fissure N=6, Faecaloma N=7, Hard faeces N=4, Anal skin tags N=1, Rhinorrhoea N=1
Uhm 2007	SAE None AE Number of children with an AE: 2/24	SAE None AE Number of children with an AE: 5/32

	Nausea N=1, Diarrhea N=1	Nausea N=1, Diarrhea N=2, Abdominal discomfort N=2
Voskuijl 2004	SAE None AE NR	SAE None AE NR
Wang 2007	SAE None AE NR	SAE None AE NR
PEG vs Magnesium hydroxide		
Gomes 2011	SAE NR AE NR	SAE NR AE NR
Loening-Baucke 2006	SAE None AE NAR. Allergic N=1 Transient diarrhea which disappeared with dose reduction was reported. Not reported per group.	SAE None AE NAR Transient diarrhea which disappeared with dose reduction was reported. Not reported per group.
Ratanamongkol 2009	SAE None AE Number of children with an AE: 20/46 Number of children with specific AE: Diarrhoea N=2, Abdominal pain N=9, bloating N=13, nausea N=4	SAE None AE Number of children with an AE: 24/43 Number of children with specific AE: Diarrhoea N=12, abdominal pain N=14, Bloating N=13, Nausea N=9
PEG vs Dietary		
Quitadamo 2012 *Fiber mixture*	SAE NR	SAE NR

	AE None	AE None
PEG 4000 vs PEG3350 + electrolytes		
Bekkali 2018	SAE Number of children with a SAE: 0/49 AE Number of children with an AE: 28/49 Number of children with specific AE: Abdominal pain N=3, Diarrhoea N=1, Mouth ulceration N=1, Nausea N=2, Vomiting N=4, Influenza like illness N=1, Pyrexia N=9, Ear infection N=1, Gastroeneritis N=2, Gastroenterisitis viral N=3, Influenza N=2, Nasopharyngitis N=5, Respiratory tract infection N=2, Upper respiratory tract infection N=3, Urinary tract infection N=1, Varicella N=1, Viral infection N=1, Headache N=3, Polyuria N=1, Oropharyngeal pain N=2, Eczema N=1	SAE Number of children with a SAE: 2/48 Prevalence of AE's: Dehydration N=2, Upper respiratory infection N=1, Metabolic acidosis N=1, Constipation N=1 AE Number of children with an AE: 28/48 Number of children with specific AE: Diarrhoea N=1, Nausea N=3, Toothache N=1, Vomiting N=2, Influenza like illness N=1, Pyrexia N=4, Bronchitis N=2, Ear infection N=1, Eye infection N=1, Gastroenteritis N=5, Gastroenteritis viral N=3, Influenza N=1, Nasopharyngitis N=4, Pseudocroup N=2, Upper respiratory tract infection N=1, Urinary tract infectrion N=1, Varicella N=3, Viral infection N=1, Dehydration N=1, Headache N=1, Polyuria N=1, Cough N=1, Eczema N=1
Savino 2012	SAE NR AE Number of children with an AE: 1/50 Diarrhoea and vomiting N=1	SAE NR AE Number of children with an AE: 1/46 Abdominal pain N=1
PEG vs herbal medicine		
Dehghani 2019 *Black strap molasses (BSM) (sugarcane extract)*	SAE NR AE Number of children with an AE: 7/47 Abdominal pain N=7	SAE NR AE Number of children with an AE: 4/45 Abdominal pain N=4
Esmaeilidooki 2016 *Cassia's fistula emulsion*	SAE NR AE	SAE NR AE

	Number of children with specific AE: Diarrhoea N=15/57, Abdominal pain N=5/57	Number of children with specific AE: Diarrhoea N=13/52, Abdominal pain 2/52
Imanieh 2022 *R. damascena and brown sugar syrup*	NAR	NAR
Nasri 2022 *LaxaPlus Barij®*	NR	NR
Nimrouzi 2015 *D. Sohpia seed*	NR 10 patients received bisacodyl suppositories after seven days of no bowel movement. Unlcear if these cases were new onset.	NR 3 patients received bisacodyl suppositories after seven days of no bowel movement. Unlcear if these cases were new onset.
Saneian 2021 *Goleghand®*	NR	NR
Tavassoli 2021 *Viola flower syrup*	<u>SAE</u> NR <u>AE</u> Number of patients with specific AE: Abdominal pain N=6, Loose stools N=2, Nausea N=2, Vomiting N=1, Unpleasant taste N=2	<u>SAE</u> NR <u>AE</u> Number of patients with specific AE: Abdominal pain N=1, Unpleasant taste N=1
PEG vs liquid paraffin		
Karami 2009	NAR	NAR
Rafati 2011	NR	NR
PEG vs microenema		
Strisciuglio 2021 *Enema: Promelaxin*	<u>SAE</u> Number of children with an SAE: 0/77 <u>AE</u> Number of events reported by patients: N=107	<u>SAE</u> Number of children with an SAE: 2/76 Type of SAE not reported <u>AE</u> Number of events reported by patients: N=76
Enema as addition to PEG		
Bongers 2009 *Enema: sodium-dioctyl sulfosuccinate and sorbitol*	NR	NR
PEG vs prebiotics vs probiotics		

Foroughi 2022 *Prebiotics: psyllium* *Probiotics: L.reuteri, L. rhamnosus, and Bifidobacterium infantis*	NR	NR
PEG vs sodium picosulfate (SP) vs dietary		
Cassetari 2019 *Dietary: green banana biomass (GBB)*	<u>SAE</u> PEG: none PEG + GBB: none <u>AE</u> PEG: none PEG + GBB: none	<u>SAE</u> SP: none GBB: none SP + GBB: none <u>AE</u> SP: none GBB: none SP + GBB: none
PEG vs dry cupping		
Shahamat 2016	NR	NR
Lactulose vs placebo		
Cao 2018	<u>SAE</u> 0/50 <u>AE</u> Number of children with specific AE: anal dilatation N=11/50, upper respiratory tract infections N=8/50, fecaloma N=9/50, anal fissure N=7/50, hard feces N=4/50, rhinorrhea N=1/50	<u>SAE</u> 0/50 <u>AE</u> Number of children with specific AE: anal dilatation N=8/50, upper respiratory tract infections N=6/50, fecaloma N=6/50, anal fissure N=5/50, hard feces N=2/50, rhinorrhea N=2/50
Lactulose vs dietary		
Kokke 2008 *Fiber mixture*	<u>SAE</u> 0/70 <u>AE</u> Number of children with an AE: 2/70 Persistent diarrhea N=2	<u>SAE</u> 0/65 <u>AE</u> Number of children with an AE: 1/65 Persistent diarrhea N=1
Ustundag 2010 *Partially hydrolysed guargum (PHG)*	NR	NR
Lactulose vs liquid paraffin		

Farahmand 2007	SAE 0/120 AE NAR (only data in figure, no numbers) "Significantly more adverse events were reported by patients using lactulose compared with patients on liquid paraffin."	SAE 0/127 AE NAR (only data in figure, no numbers)
Urganci 2005	SAE NR AE NAR (adverse events only reported in context of how it influenced compliance, not as outcome)	SAE NR AE NAR (adverse events only reported in context of how it influenced compliance, not as outcome)
Lactulose vs lactitol		
Pitzalis 1995	NR	NR
Lactulose vs probiotics		
Lee 2022 *S. boulardii*	SAE NR AE NAR (not reported per group)	SAE NR AE NAR (not reported per group)
Olgac 2013 *L. reuteri*	SAE NR AE NAR (not reported per group)	SAE NR AE NAR (not reported per group)
Lactulose as addition to PEG		
Ala 2015	SAE NR AE	SAE NR AE Number of children with an AE: 0/100

	Number of children with an AE: 15/100 "Adverse effects such as abdominal pain, diarrhea, and flatulence". Not reported how many per adverse event.	
Magnesiumoxide vs probiotics		
Bu 2007 Compares MgO vs probiotics vs placebo *Probiotics: L. rhamnosus lcr35*	<u>SAE</u> NR <u>AE</u> Number of children with an AE: 1/18 Mild diarrhea N=1	<u>SAE</u> NR <u>AE (Probiotics)</u> Number of children with an AE: 0/18 <u>AE (Placebo)</u> Number of children with an AE: 0/9
Kubota 2020 *Compares MgO vs probiotics vs MgO + probiotics* *Probiotics: L. reuteri*	<u>SAE</u> NR <u>AE</u> NAR (only reported that no AE's related to any treatment was observed)	<u>SAE</u> NR <u>AE</u> NAR (only reported that no AE's related to any treatment was observed)
Liquid paraffin vs herbal medicine		
Mozaffarpur 2012 *Cassia fistula emulsion*	<u>SAE</u> 0/40 <u>AE</u> Number of children with a specific AE: Anal oily leakage N=27/40, abdominal pain N=3/40, extra saliva N=2/41, headache N=1/40, drug intolerance accompanied with upper respiratory infection N=1	<u>SAE</u> 0/41 <u>AE</u> Number of children with a specific AE: Diarrhea N=12/40, abdominal pain N=3/41, sputum-like stool N=1/41
Liquid paraffin vs synbiotics		
Khodadad 2010 *Multispecies probiotics + fructo-oligosaccharides*	NR	NR
Lubiprostone vs placebo		
Benninga 2022	<u>SAE</u> 11/400 Hepatotoxicity N=1, Anaphylactoid reaction N=1, Decreased consciousness N=1, Dehydration and IBS-C N=1, Fecaloma and	<u>SAE</u> 7/195 NR

	rash N=1, Fecaloma N=2, Ulcerative colitis N=1, Suicidal ideation N=2, Coxsackie virus N=1 <u>AE</u> Number of children with an AE: 239/400 AE's occurring in >5% of children: headache N=34/400, Nausea N=257/400, Vomiting N=45/400, Abdominal pain N=42/400	<u>AE</u> Number of children with an AE: 114/195 AE's occurring in >5% of children: headache N=10/195, nausea N=14/195, vomiting N=12/195, abdominal pain N=23/195
Prucalopride vs placebo		
Mugie 2014	<u>SAE</u> Number of children with a SAE: 5/106 Number of children with specific SAE: abdominal pain N=1, vomiting N=, diarrhea N=1, Nausea N=1, Appendicitis N=1, Pneumonia N=1, Dizziness N=1, Syncope N=1, Anxiety N=1 <u>AE</u> Number of children with an AE: 101/106 Number of children with specific AE: Headache N=17, Pyrexia N=15, Abdominal pain N=14, Vomiting N=15, Nausea N=10, Viral infection N=6, Cough N=6, Diarrhea N=6, Nasopharyngitis N=3, Pharyngitis N=3, Bronchitis N=2, Upper respiratory tract infection N=2, Constipation N=2	<u>SAE</u> Number of children with a SAE:2/107 Number of children with specific SAE: Abdominal pain N=1, Constipation N=1, Anorectal discomfort N=1 <u>AE</u> Number of children with an AE: 72/107 Number of children with specific AE: Headache N=9, Pyrexia N=3, Abdominal pain N=13, Vomiting N=5 Nausea N=6, Viral infection N=5, Cough N=2 Diarrhea N=6, Nasopharyngitis N=2, Pharyngitis N=6 Bronchitis N=7, Upper respiratory tract infection N=5, Constipation N=3
Linaclotide vs placebo		
Di Lorenzo 2020	<u>SAE</u> Number of children with a SAE: 0/39 <u>AE</u> Number of children with an AE: 15/39 Not reported for all AE's. Diarrhea N=4, Headache N=4, fecaloma N=2	<u>SAE</u> Number of children with a SAE: 0/41 <u>AE</u> Number of children with an AE: 9/41 Not reported for all AE's. Headache N=1, vomiting N=1, alanine aminotransferase increased N=1, aspartate aminotransferase increased N=1
Di Lorenzo 2024	<u>SAE</u> Number of children with a SAE: 2/164 Diarrhea N=1, Faecaloma N=1 <u>AE</u> Number of children with an AE: 28/164	<u>SAE</u> Number of children with a SAE: 2/164 Suicide attempt N=2, suicidal ideation N=1 <u>AE</u> Number of children with an AE: 35/164

	Number of children with a Treatment Related AE: diarrhea N=6, Nausea N=2, Abdominal discomfort N=1, COVID-19 N=1, dehydration N=1	Number of children with a Treatment related AE: diarrhea N=2, abdominal distention N=1, dizziness N=1, headache N=1
Domperidone as addition to PEG		
Dehghani 2014	SAE NR AE Number of children with an AE: 0/52	SAE NR AE Number of children with an AE: 0/52

NR: Not reported, NAR: not adequately reported

Appendix 12. Bijwerkingen studies niet-medicamenteuze behandeling

Study	Intervention	Control
Probiotics vs placebo		
Lojanatorn 2023	SAE 0/21 AE Number of children with an AE: 3/21 Urticaria N=1, abdominal pain N=1, dropout due to severe abdominal N=1	SAE 0/18 AE Number of children with an AE: 1/18 Vomiting N=1
Tabbers 2011	SAE Not reported per group: 2 SAE's, probably not related to consumption of the study drugs occurred Broken arm N=1, gynecological pain caused by a gynecological cyst N=1 AE Number of children with an AE: 4/79 Gastroenteritis N=1, nausea/vomiting N=3	SAE Not reported per group: 2 SAE's, probably not related to consumption of the study drugs occurred Broken arm N=1, gynecological pain caused by a gynecological cyst N=1 AE Number of children with an AE: 6/80 Gastroenteritis N=3, nausea/vomiting N=2, candida-infection of anorectal region N=1
Tjokronegoro 2020	SAE 0/39 AE Number of children with an AE: 2/39 Mild abdominal pain N=2	SAE 0/39 AE Number of children with an AE: 6/39 Mild abdominal pain N=4, mild diarrhea N=2
Zaja 2021	SAE 0/15 AE Number of children with an AE: 0/15	SAE 0/16 AE Number of children with an AE: 0/16
Bu 2007 *L. rhamnosus lcr35 vs placebo vs MgO*	NR	NR

Wojtyniak 2017	SAE 0/48 AE Number of children with an AE: 0/48	SAE 0/46 AE Number of children with an AE: 3/46 Change in stool odor N=1, abdominal pain and flatulence N=1, loss of appetite N=1
Gan 2022	NR	NR
Coccorullo 2010	NR	NR
Probiotics vs laxative		
Kubota 2020 *L. reuteri vs MgO*	SAE NR AE Number of children with an AE: 0/20	SAE NR AE Number of children with an AE: 0/21
Lee 2022 *S. boulardii vs Lactulose*	SAE NR AE Number of children with an AE: NR per group and per patient. Abdominal pain = 20.9%, 11.3%, and 1.8% at weeks 2, 6, and 12, respectively. Diarrhea = 6.3% and 4.7% at weeks 2 and 6, respectively. Abdominal distension = 4.4% at week 2, and Vomiting = 1.3% at week 2). There were no intergroup differences.	SAE NR AE Number of children with an AE: NR per group and per patient. Abdominal pain = 20.9%, 11.3%, and 1.8% at weeks 2, 6, and 12, respectively. Diarrhea = 6.3% and 4.7% at weeks 2 and 6, respectively. Abdominal distension = 4.4% at week 2, and Vomiting = 1.3% at week 2). There were no intergroup differences.
Olgaç 2013 *L. reuteri vs lactulose*	SAE NR AE Number of children with an AE: 0/25	SAE NR AE Number of children with an AE: 0/28
Probiotics as addition to laxatives		
Abediny 2016 *Multispecies and PEG*	NR	NR

Banaszkiewicz 2005 *Lactobacillus GG and lactulose*	SAE NR AE Number of patients with an AE: 4/43 Abdominal pain N=3, vomiting N=1	SAE NR AE Number of patients with an AE: 6/41 5 abdominal pain, 1 head ache
Jadrešin 2018 *L. reuteri and lactulose*	SAE NR AE Number of patients with an AE: 0/18	SAE NR AE Number of patients with an AE: 0/18
Foroughi 2022 *Laxative: PEG* *Prebiotics: psyllium* *Probiotics: L.reuteri, L. rhamnosus, and Bifidobacterium infantis*	NR	NR
Kubota 2020 *Multispecies and Magnesiumoxide*	NR	NR
Russo 2017 *Multispecies and PEG*	No data reported No significant clinical adverse effects, except for transient diarrhea, which disappeared with dose reduction	No data reported No significant clinical adverse effects, except for transient diarrhea, which disappeared with dose reduction
Sadeghzadeh 2014 *Multi species and lactulose*	SAE NR AE Number of patients with an AE: 0/28	SAE NR AE Number of patients with an AE: 0/28
Wegner 2018 *L. reuteri + PEG*	SAE 0/65 AE Number of patients with an AE: 2/65 Abdominal pain N=2	SAE 0/64 AE Number of patients with an AE: 2/65
Probiotics as addition to goat yoghurt		

Guerra 2011	NR	NR
Formula 1 intact protein + PEG vs Formula 2 hydrolyzed whey + PEG		
Sevilla 2022	SAE Number of children with an AE: 0/47 AE Number of patients with an AE: 0/47	SAE Number of children with an AE: 0/48 AE Number of patients with an AE: 0/48
Herbal medicine vs laxative		
Dehghani 2019 *Black strap molasses (sugarcane extract) vs PEG*	SAE NR AE Number of patients with an AE: 4/45 Abdominal pain N=4	SAE NR AE Number of patients with an AE: 7/47 Abdominal pain N=7
Esmaeilidooki 2016 *Cassia's fistula emulsion vs PEG*	SAE NR AE Number of patients with an AE: 15/52 Diarrhoea N=13, abdominal pain N=2	SAE NR AE Number of patients with an AE: 20/66 Diarrhoea N=15, abdominal pain N=5
Imanieh 2022 *R. damascena and brown sugar syrup vs PEG*	SAE NR AE Number of patients with an AE: 0/50	SAE NR AE NR
Mozaffarpur 2012 *Cassia fistula emulsion vs Liquid Paraffin*	NR	NR
Nasri 2022 *LaxaPlus Barij® vs PEG*	NR	NR
Nimrouzi 2015 *D. Sohpia seed vs PEG*	NR	NR
Saneian 2021 *Goleghand® vs PEG*	NR	NR
Tavassoli 2021 *Viola flower syrup vs PEG*	SAE NR	SAE NR

	AE Number of patients with an AE: 1/67 Abdominal pain N=1	AE Number of patients with an AE: 12/66 6 abdominal pain N=6, loose stools N=2, nausea N=2, vomiting N=1
Herbal medicine vs placebo		
Cai 2018	SAE NR AE Number of patients with an AE: 7/360 Type of adverse events not reported for all adverse events and for which group. Only ones reported were: loose stool N=1, diarrhea N= 3, and vomit N=1	SAE NR AE Number of patients with an AE: 2/120 Type of adverse events not reported for all adverse events and for which group. Only ones reported were: loose stool N=1, diarrhea N= 3, and vomit N=1
Manual physical therapy vs laxative		
Blanco Diaz 2020 Laxative: PEG	NR	NR
Cow's milk free diet vs cow's milk diet		
Iacono 1998	NR	NR
Dehghani 2012	NAR	NAR
Cow's milk free diet + PEG vs PEG		
Bourkheili 2021	NR	NR
Formula 1 (partially hydrolyzed cow's milk protein) + prebiotics mix vs Formula 2 (cow's milk-based) vs prebiotics mix		
Fabrizio 2022	SAE NR AE Number of patients with an AE: 14/42 No reasons provided	SAE NR AE Number of patients with an AE: 8/47 No reasons provided
Increased water intake vs hyperosmolar liquid vs control		

Young 1998	NR	NR
Parasacral transcutaneous nerve stimulation (PTENS) vs sham therapy		
De Abreu 2021	NR	NR
Abdominal transcutaneous electrical stimulation vs sham therapy		
Clarke 2009	NR	NR
Abdominal transcutaneous electrical stimulation as addition to pelvic floor muscle exercise		
Sharifi-Rad 2018	<u>SAE</u> NR <u>AE</u> Number of patients with an AE: 0/45	<u>SAE</u> NR <u>AE</u> Number of patients with an AE: 0/45
Lady-Seyedian 2020	<u>SAE</u> NR <u>AE</u> Number of patients with an AE: 0/17	<u>SAE</u> NR <u>AE</u> Number of patients with an AE: 0/17
Abdominal transcutaneous electrical stimulation and cryotherapy and standard therapy		
Khan 2020	NR	NR
Tibial nerve stimulation as addition to Pelvis Floor Exercises		
Yu 2023	<u>SAE</u> 0/42 <u>AE</u> Number of patients with an AE: 3/42 Skin allergies + erythema + blisters N=1 and foot numbness N=2	<u>SAE</u> 0/42 <u>AE</u> Number of patients with an AE: 4/42 Skin allergies + erythema + blisters N=2 and foot numbness N=2
Self-monitoring and reward system to increase fiber intake vs standard dietary advice		
Sullivan 2012	NR	NR
Additional effect of behavioral therapy to laxatives		
Van Dijk 2008	NR	NR

Biofeedback vs no biofeedback		
Castilla 2021 (abstract only)	NR	NR
Additional effect of biofeedback to laxatives		
Loening-Baucke 1990 *Vs magnesiumhydroxide*	NR	NR
Sunic-Omejc 2002 *vs Lactulose*	NR	NR
Van der Plas 1996 *vs lactitol*	NR	NR
Additional effect of biofeedback at home to biofeedback in laboratory setting		
Croffie 2005	NR	NR
Fiber vs placebo		
Chmielewska 2011 *Glucomannan*	SAE 1/40 Rotavirus acute gastroenteritis requiring hospital admission for intravenous rehydration N=1. AE Number of patients with an AE: NR Total of adverse events: Gastroenteritis N=1, Vomiting N=1, Bronchitis N=2, Otitis media N=1	SAE 0/40 AE Number of patients with an AE: NR Total of adverse events: Gastroenteritis N=2, Vomiting N=1, Bronchitis N=1, Pruritus N=1
Loening-Bauke 2004 *Glucomannan*	SAE 0/27 AE Number of patients with an AE: 0/27	SAE 0/19 AE Number of patients with an AE: 0/19
Weber 2014 *Fiber mixture*	SAE 0/27 AE NR	SAE 0/30 AE NR
Fiber vs laxatives		

Kokke 2008 *Fiber mixture vs lactulose*	SAE 0/65 AE Number of children with an AE: 1/65 Persistent diarrhea N=1	SAE 0/70 AE Number of children with an AE: 2/70 Persistent diarrhea N=2
Üstündağ 2010 *Partially hydrolysed guargum vs lactulose*	NR	NR
Cassetari 2019 *Green banana biomass vs PEG and vs Sodium Picosulfate*	SAE GBB: 0/15 AE GBB: 0/15	SAE PEG: 0/16 SP: 0/17 AE PEG: 0/16 SP: 0/17
Quitadamo 2012 *Fiber mixture vs PEG*	SAE NR AE 0/36	SAE NR AE 0/47
Prebiotics vs placebo		
Da Silva Souza 2018	SAE NR AE Number of children with an AE: 4/19 Pneumonia N=1, abdominal distention and flatulence N=2, vomiting N=1	SAE NR AE Number of children with an AE: 0/19
Formula with prebiotic and hydrolyzed whey protein vs standard formula		
Savino 2005 *Galactooligosaccharides and fructo-oligosaccharides*	SAE 0/69 AE Number of children with an AE: 0/69	SAE 0/54 AE Number of children with an AE: 0/54
Bongers 2007 *Galactooligosaccharides*	SAE 0/20	SAE 0/15

and *fructo-oligosaccharides*	 AE Number of children with an AE: 0/20	 AE Number of children with an AE: 0/15
Synbiotics vs placebo		
Baştürk 2017	SAE NR AE Number of children with an AE: 0/77	SAE NR AE Number of children with an AE: 0/78
Synbiotics vs laxative		
Khodadad 2010 *Multispecies probiotics + fructo-oligosaccharides* *Laxative: liquid paraffin*	NR	NR
Abdominal and acupressure point massage as addition to traditional Chinese medicine		
Mao 2015	NR	NR
Xu 2015	NR	NR
Foot reflexology massage as addition to toilet/diet/motivation training		
Canbulat Sahiner 2017	NR	NR
Pelvic physiotherapy as addition to standard medical care		
Van Engelenburg 2017 *52/53 patients received PEG*	NR	NR
Abdominal muscle training/breathing exercises/abdominal massage as addition to laxatives		
Silva 2013 *Laxative: Magnesium Hydroxide (MgO)*	NR	NR
Dry cupping vs laxative		
Shahamat 2016 *PEG*	NR	NR

SAE: serious adverse event, AE: adverse event, NR: not reported

Appendix 13. Risk of Bias beoordeling geïncludeerde artikelen initiële medicamenteuze behandeling

Bekkali 2009	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Author confirmed computer-generated randomisation.
Allocation concealment (selection bias)	Low risk
	Author responded that they used the sealed envelopes method for allocation of participants.
Blinding of participants and personnel (performance bias)	High risk
	Open label, patients and personnel could not be blinded due to differences in intervention.
Blinding of outcome assessment (detection bias)	High risk
	Open label, patients and personnel could not be blinded due to differences in intervention.
Incomplete outcome data (attrition bias)	Low risk
	All reasons for dropouts are stated.
Selective reporting (reporting bias)	High risk
	Trial registration reported (NTR602). Results reported appropriately. No safety data reported. Only abdominal pain was measured.
Other bias	Low risk
	Baseline characteristics are balanced.

Appendix 14. Risk of Bias beoordeling geïncludeerde artikelen onderhoudstherapie medicamenteuze behandeling

Ala 2015	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	dived randomly by random block of four
Allocation concealment (selection bias)	Unclear
	Nothing mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear how many drop outs per group
Selective reporting (reporting bias)	Unclear
	No protocol was found
Other bias	Low risk
	No significant differences for baseline characteristics

Bekkali 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomization numbers were generated by a licensed Clinical Research Organization
Allocation concealment (selection bias)	Low risk
	Randomization number allocation was performed by an independent employee of the clinical research organization via telephone
Blinding of participants and personnel (performance bias)	Low Risk
	Patients and study personnel were blinded. Packaging, labeling and dose per sachet were identical.
Blinding of outcome assessment (detection bias)	Low Risk
	Patients and study personnel was blinded. Packaging, labeling and dose per sachet were identical.
Incomplete outcome data (attrition bias)	High risk
	1/3rd of patients withdrew due to 'other' no further info given regarding this. >20% of intervention group withdrew. Asked author, no specific reasons available
Selective reporting (reporting bias)	Low Risk
	Key efficacy outcomes and a safety outcome reported
Other bias	Low Risk
	Baseline demographics balanced

Benninga 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Patients were assigned to treatment groups using randomization code and stratification scheme generated by the Randomization and Trial Supply Management system.
Allocation concealment (selection bias)	Low risk
	Stratification scheme generated by the Randomization and Trial Supply Management system (ClinPhone; Parexel, Waltham, MA)
Blinding of participants and personnel (performance bias)	Low risk
	Patients and parents were blinded, identical containers with and as identical soft gelatin capsules. Investigators were blinded as well.
Blinding of outcome assessment (detection bias)	Low risk
	Patients and parents were blinded, identical containers with and as identical soft gelatin capsules. Investigators were blinded as well.
Incomplete outcome data (attrition bias)	Low risk
	Reasons were reported. For some patients 'no discontinuation reason provided'. Patients were asked and didn't give a reason.
Selective reporting (reporting bias)	Low risk
	Key outcomes reported. Study per protocol.
Other bias	Low risk
	Baseline characteristics balanced

Blanco-Diaz 2020	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated random sequence
Allocation concealment (selection bias)	Low risk
	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear. Only report compliance and attendance rates. At every outcome measurement point, the number of patients differ. Unclear if patients were lost to follow-up.
Selective reporting (reporting bias)	High risk
	No protocol found. They do not mention anything about recording side effects during the study (only the Symptom Severity Score), but do say in their conclusion that Manual Therapy has no side effects.
Other bias	Low risk
	Baseline demographics balanced

Bongers 2009	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computerized randomization was used to generate a sequence of random group assignment for consecutive patients This computer program based on the biased coin method used minimization to achieve a balanced randomization on 2 factors, gender and age (13 years versus 13 years).
Allocation concealment (selection bias)	Low risk
	Contact with the authors: concealed envelopes
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	4 patients in IG group refused further application, no reasons provided. Contact with authors: patients were asked but did not provide a reason. Number too small that it could have affected the results.
Selective reporting (reporting bias)	Low risk
	The trial was registered retrospectively, authors confirmed that protocol was made prospectively. Primary outcome was reported as predefined in the protocol.
Other bias	Low risk
	Baseline demographics balanced

Bu 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer-generated randomization list
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Three interventions with similar appearances and placed into identical capsules.
Blinding of outcome assessment (detection bias)	Low risk
	Three interventions with similar appearances and placed into identical capsules
Incomplete outcome data (attrition bias)	Unclear
	Numbers per group reported, no imbalance. Reasons provided, however unclear which reasons belong to which patient/group. Two patients suffered from actue gastroenteritis, unclear in which group.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration.
Other bias	Low risk
	Baseline demographics balanced

Cao 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Low risk
	Any randomization and allocation information were concealed in opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk
	Patient and study personnel masked. Participants in the placebo group got placebo, the same size, dose, color, flavor, and appearance as the lactulose in the treatment group.
Blinding of outcome assessment (detection bias)	Low risk
	Patient and study personnel masked. Participants in the placebo group got placebo, the same size, dose, color, flavor, and appearance as the lactulose in the treatment group.
Incomplete outcome data (attrition bias)	Low risk
	All drop outs per group reported with reasons. Represented in flow diagram.
Selective reporting (reporting bias)	Unclear
	No protocol found. Key safety data and outcomes reported.
Other bias	Low risk
	Baseline demographics balanced

Cassetari 2019	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Subjects were randomly assigned into five treatment groups by a mathematical algorithm
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Patients and personnel blinded. Biomass looked identical as a thick, white, homogenous mass. No substantial variation in colour, taste, and smell.
Blinding of outcome assessment (detection bias)	Low risk
	Patients and personnel blinded. Biomass looked identical as a thick, white, homogenous mass. No substantial variation in colour, taste, and smell.
Incomplete outcome data (attrition bias)	Low risk
	All drop outs per group reported with reasons.
Selective reporting (reporting bias)	Low risk
	Key outcomes and safety data reported per protocol.
Other bias	Low risk
	Baseline demographics balanced

Dehghani 2014	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Patients were randomly assigned by a computer-generated method with the individual patient as the unit of randomization
Allocation concealment (selection bias)	Low risk
	Each regimen packed by pharmacist with a special code, so that neither the physician nor patient knew what regimen was consigned to each subject.
Blinding of participants and personnel (performance bias)	Low risk
	Both intervention and control group received treatment with the same colour, taste, and smell (as syrup). Study personnel was also blinded.
Blinding of outcome assessment (detection bias)	Low risk
	Both intervention and control group received treatment with the same colour, taste, and smell (as syrup). Study personnel was also blinded.
Incomplete outcome data (attrition bias)	Low risk
	All drop outs per group reported with reasons. Represented in flow diagram.
Selective reporting (reporting bias)	Unclear risk
	Study protocol present, but trial registration in 2013 and started including in 2011. Outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Dehghani 2019	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Low risk
	Word 'allocation' used to describe joining group without further discussion. Contacted author, answer: allocation concealment was done by numbered drug containers.
Blinding of participants and personnel (performance bias)	Low risk
	Drug and placebo prepared with similar organoleptic properties; packaged in identical containers. Patients and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk
	Drug and placebo prepared with similar organoleptic properties; packaged in identical containers. Patients and personnel blinded.
Incomplete outcome data (attrition bias)	Low risk
	Flow of patients including randomised and assessed, drop outs reported with reasons given in flow chart.
Selective reporting (reporting bias)	Low risk
	Key outcomes and safety data reported per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Dheivamani 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block Randomisation via computer-generated codes
Allocation concealment (selection bias)	Low risk
	Allocation concealment performed using sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk
	Open label trial
Blinding of outcome assessment (detection bias)	Low risk
	Open label trial
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart
Selective reporting (reporting bias)	Low risk
	Key outcomes and safety outcomes reported per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Dupont 2005	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Randomisation but with no specified method - only reference to a 'randomisation list'
Allocation concealment (selection bias)	Unclear
	States randomly allocated but no specific detail.
Blinding of participants and personnel (performance bias)	Low risk
	Double-dummy design due to difference in taste
Blinding of outcome assessment (detection bias)	Low risk
	Double-dummy design
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart
Selective reporting (reporting bias)	Unclear
	No protocol found but key outcomes and safety data reported.
Other bias	Low risk
	Baseline demographics balanced.

Di Lorenzo 2020 (abstract only)	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Low risk
	Central allocation
Blinding of participants and personnel (performance bias)	Low risk
	Participant, Care Provider, Investigator, Outcomes Assessor were blinded. Matching placebo.
Blinding of outcome assessment (detection bias)	Low risk
	Participant, Care Provider, Investigator, Outcomes Assessor were blinded. Matching placebo.
Incomplete outcome data (attrition bias)	Low risk
	After answer of author: drop outs equal between groups and reasons reported.
Selective reporting (reporting bias)	Low risk
	After answer of authors: Key outcomes and safety outcomes reported as per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Di Lorenzo 2024	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomisation was by block randomisation (block size four)
Allocation concealment (selection bias)	Low risk
	Assigned (1:1) by use of an interactive web response system (IWRS; Premier Research International Interactive Response Technologies, East Hartford, CT, USA) to receive either linaclotide or placebo. A sponsor randomization personnel generated the randomisation schedule and provided it to IWRS for implementation. The randomization sequence was not visible to any staff at the investigational site.
Blinding of participants and personnel (performance bias)	Low risk
	Linaclotide and placebo were provided in matching capsules with identical appearance. Participants, site investigators, study outcome assessors, and bioanalytical representatives (ie, those analysing the data) were masked to study treatment
Blinding of outcome assessment (detection bias)	Low risk
	Linaclotide and placebo were provided in matching capsules with identical appearance. Participants, site investigators, study outcome assessors, and bioanalytical representatives (ie, those analysing the data) were masked to study treatment
Incomplete outcome data (attrition bias)	Low risk
	Dropout rate balanced, and reasons provided in flow-chart
Selective reporting (reporting bias)	Low risk
	Study and outcomes reported per protocol
Other bias	Low risk
	Baseline demographics balanced

Esmaeilidooki 2016	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Stated 'Simple Randomisation' without specified method.
Allocation concealment (selection bias)	Unclear
	Stated 'Random allocation' without specified method.
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety data and outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Farahmand 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Unclear how randomisation occurred.
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Unclear
	No drop outs reported but 'lost to follow up' mentioned in
Selective reporting (reporting bias)	Unclear
	No protocol. Key safety data and outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Foroughi 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Simple Randomisation method used to divide patients into 4 groups. No specified method.
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk
	Drugs were prepared in identical packages and unlabelled sachets with only codes. patient and researcher were blinded. no mention of taste differences between the interventions.
Blinding of outcome assessment (detection bias)	Low risk
	As above
Incomplete outcome data (attrition bias)	Unclear
	Not mentioned.
Selective reporting (reporting bias)	Unclear
	Protocol, key outcomes present. Safety Data not reported
Other bias	Low risk
	Baseline demographics balanced. But do miss 3 patients in group B.

Gomes 2011	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Mentions randomisation without specified method. Contacted authors: low tech (coins heads or tails)
Allocation concealment (selection bias)	Unclear
	Not mentioned. Contacted authors: still unclear.
Blinding of participants and personnel (performance bias)	High risk
	Non-blind Trial
Blinding of outcome assessment (detection bias)	High risk
	Non-blind Trial
Incomplete outcome data (attrition bias)	High risk
	Losses reported but no reason given. No flow chart.
Selective reporting (reporting bias)	High risk
	Protocol available. No Safety Data reported.
Other bias	Low risk
	Baseline demographics balanced.

Imanieh 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Permuted block randomization was used for randomly allocating the participants to the two groups.
Allocation concealment (selection bias)	Low risk
	Allocation concealment was achieved using the dark envelope method.
Blinding of participants and personnel (performance bias)	Low risk
	Containers with the same shape, colour, and weight, so that the containers and solutions would not be distinguishable (no mention of taste). The patients, physicians, and the analyst were not aware of the ingredients of the solutions, only the pharmacist.
Blinding of outcome assessment (detection bias)	Low risk
	Containers with the same shape, colour, and weight, so that the containers and solutions would not be distinguishable (no mention of taste). The patients, physicians, and the analyst were not aware of the ingredients of the solutions, only the pharmacist
Incomplete outcome data (attrition bias)	Low risk
	Reasons provided. No imbalance in number of patients per group (6 vs 2)
Selective reporting (reporting bias)	Unclear
	Primary outcome in paper: not fulfilling Rome IV criteria anymore. In protocol primary outcomes are all Rome IV criteria (and more) separately.
Other bias	High risk
	Most of the baseline demographics balanced. Duration of functional constipation differs between groups: 74% of IG and 44% CG had been suffering from functional constipation for more than 12 months.

Jarzebicka 2019	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Low risk
	The investigators faxed a request for randomization to central randomization centre (CRC). Study staff assigned the patient to the appropriate place on the list according to centre and block to learn the randomization arm. In return, treating physicians received a fax back with the treatment arm for the patient.
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Withdrawals reported with partial explanations. No reasons given for other.
Selective reporting (reporting bias)	Low risk
	Study protocol present. Key outcomes and safety data reported.
Other bias	Low risk
	Baseline demographics balanced.

Karami 2009	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Mentions systematic and random sampling. Unclear how.
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Single blinded. Unclear how blinded and medication vastly different and as such would likely make high risk
Blinding of outcome assessment (detection bias)	High risk
	Single blinded. Unclear how blinded and medication vastly different and as such would likely make high risk
Incomplete outcome data (attrition bias)	High risk
	No reasons reported for dropouts
Selective reporting (reporting bias)	High risk
	No protocol found. Safety was not an outcome measure in this study. 4month follow up data not reported
Other bias	Unclear
	Not all baseline data reported per group (eg. age). Also unclear if reported baseline data is for all randomized patients.

Khodadad 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Randomisation was generated by their biostatistics consultant. However, unclear how randomisation occurred.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Unclear
	Physicians and nurses were blinded. Bottles and sachets were similar in shape, taste and colour. Only label indicating A or B. However: Group A received 1.5 ml/kg/day oral liquid paraffin plus placebo, group B received 1 sachet synbiotic per day, Group C received 1.5 ml/kg/day oral liquid paraffin and 1 sachet synbiotic per day. Group B seemed to only receive a sachet with synbiotics, no placebo for laxative.
Blinding of outcome assessment (detection bias)	Unclear
	Physicians and nurses were blinded. Bottles and sachets were similar in shape, taste and colour. Only label indicating A or B. However: Group A received 1.5 ml/kg/day oral liquid paraffin plus placebo, group B received 1 sachet synbiotic per day, Group C received 1.5 ml/kg/day oral liquid paraffin and 1 sachet synbiotic per day. Group B seemed to only receive a sachet with synbiotics, no placebo for laxative.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart with reasons.
Selective reporting (reporting bias)	Low risk
	Key outcomes (efficacy and safety) reported as per protocol
Other bias	Low risk
	Baseline characteristics balanced

Kokke 2008	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Use of sequential numbers allocated to the patients at study entry and coordinated by the logistics manager of Numico Research using a block design.
Allocation concealment (selection bias)	Unclear
	Nothing mentioned
Blinding of participants and personnel (performance bias)	Low risk
	Patients and personnel blinded. Clear description of how both interventions were packed and prepared. Products could not be distinguished.
Blinding of outcome assessment (detection bias)	Low risk
	Patients and personnel blinded. Clear description of how both interventions were packed and prepared. Products could not be distinguished.
Incomplete outcome data (attrition bias)	Low Risk
	Flow-diagram with reasons.
Selective reporting (reporting bias)	Unclear
	No protocol found.
Other bias	Unclear
	Baseline characteristics only reported for patients who reached end of study.

Kubota 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk
	All caregivers, patients, research staff, and physicians were blinded to which treatment group the patients belonged. Identical matching placebo and probiotic. bottles were matched and taste/texture were matched.
Blinding of outcome assessment (detection bias)	Low risk
	All caregivers, patients, research staff, and physicians were blinded to which treatment group the patients belonged. Identical matching placebo and probiotic. bottles were matched and taste/texture were matched.
Incomplete outcome data (attrition bias)	Unclear
	Unclear to which group the excluded patients belonged to. Only 3 patients.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Lee 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomization was implemented automatically using Random Allocation Software 2.0 (Informer Technologies, Inc, Dallas, TX, USA) with a random block size
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	High risk
	High amount of drop-outs, imbalance > 20% and reasons not specified for each group
Selective reporting (reporting bias)	Low risk
	Protocol found. Key outcomes reported as per protocol. Safety data also reported in study.
Other bias	Low risk
	"There were no differences in age, disease duration, or other clinical characteristics among the 3 groups." There were sex differences between combination therapy and s. boulardii. They adjusted for sex in their Cox Regression analysis.

Loening-Baucke 2006	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Mentions randomization, but not how
Allocation concealment (selection bias)	Low risk
	Randomization was performed by children drawing a sealed envelope with an enclosed assignment.
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Flow diagram with drop-outs reported and reasons provided. Imbalance in number of dropouts, however due to difference in drug.
Selective reporting (reporting bias)	Unclear
	No protocol found.
Other bias	Low risk
	Baseline demographics balanced.

Modin 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer-generated randomization blocks of 10 children
Allocation concealment (selection bias)	Unclear
	Unclear if the investigational drug pharmacist was not involved and pharmacist was not blinded for age/weight.
Blinding of participants and personnel (performance bias)	Low risk
	Drugs had similar taste and consistency, identical packaging. Children, parents, and investigators were blinded.
Blinding of outcome assessment (detection bias)	Low risk
	Drugs had similar taste and consistency, identical packaging. Children, parents, and investigators were blinded.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for dropout provided. No imbalance in dropouts.
Selective reporting (reporting bias)	Low risk
	According to protocol. Only safety was not included in protocol, but was an outcome in article.
Other bias	Low risk
	Baseline demographics balanced

Mozaffarpur 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Systematic randomisation
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Low risk
	Key outcomes (efficacy and safety) reported as per protocol
Other bias	Low risk
	Baseline characteristics balanced

Mugie 2014	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomization was organized using a central interactive web-based, voice-response system, which applied a minimization algorithm and generated a medication number to ensure blinding.
Allocation concealment (selection bias)	Low risk
	Author answered: pharmacy allocated the drugs
Blinding of participants and personnel (performance bias)	Low risk
	Patients and investigators were blinded to treatment allocation. Placebo was identical in taste and appearance to prucalopride.
Blinding of outcome assessment (detection bias)	Low risk
	Patients and investigators were blinded to treatment allocation. Placebo was identical in taste and appearance to prucalopride.
Incomplete outcome data (attrition bias)	Low risk
	Reasons mentioned per patient and per group, no imbalance in number of dropouts
Selective reporting (reporting bias)	Low risk
	Key outcomes reported. Study as per protocol
Other bias	Low risk
	Baseline characteristics balanced.

Nasri 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not clear how patients were randomly assigned
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	No drop outs reported.
Selective reporting (reporting bias)	High risk
	Protocol available. However, safety data not reported, was described in protocol as a secondary outcome + in methods section.
Other bias	Low risk
	Baseline demographics balanced

Nimrouzi 2015	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomization
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Reasons per group reported. No imbalance per group.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Baseline characteristics not reported for all included patients, only the ones that reached study end.

Nurko 2008	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomisation by random blocks of 20 patients
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	No difference in color, appearance, or taste among different dosages and placebo. Identical bottles. Research team and patients were blinded.
Blinding of outcome assessment (detection bias)	Low risk
	No difference in color, appaearance, or taste among different dosages and placebo. Identical bottles. Research team and patients were blinded
Incomplete outcome data (attrition bias)	Low risk
	Reason for drop-out reported per patient and no imbalance.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Olgac 2013	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random, but not how random occurred
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Pitzalis 1995	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Unclear how randomisation occurred
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Reasons not reported per group
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Baseline characteristics only reported for patietns who reachted study end

Quitadamo 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomly assigned according to an automatically generated randomization list
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Clear reasons for drop-out per patient. Difference between both groups > 20%, but this is a result of the difference in drug (bad taste).
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Rafati 2011	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Random table was used to randomize the patients
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	High risk
	Unclear reasons for drop-outs in liquid paraffin group
Selective reporting (reporting bias)	High risk
	No protocol found. Table 3: "need to additive drugs". However nothing was reported in methods section about additive drugs (evidence of plan deviation).
Other bias	Unclear
	Baseline characteristics only reported for patients that made study end

Ratamangkol 2009	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer-generated randomization list in mix block sizes by a nonparticipating statistician.
Allocation concealment (selection bias)	Low risk
	Treatment allocation was prepared in separated sealed, opaque sequentially numbered envelops. Dispensed by a blinded nurse.
Blinding of participants and personnel (performance bias)	High risk
	Could not be blinded, because medications were administered to children in different ways.
Blinding of outcome assessment (detection bias)	High risk
	Could not be blinded, because medications were administered to children in different ways.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are reported. Drop-outs equal per group.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Baseline characteristics only reported for patients who reached study end

Saneian 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Systematic randomization using the randomization software
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear how many patients randomized, nothing mentioned about dropouts
Selective reporting (reporting bias)	High risk
	No protocol found. Treatment success was not reported as how it was predefined in the methods. Safety was not described as an outcome in methods, but side effects are reported in results section.
Other bias	Low risk
	Baseline demographics balanced

Saneian 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomization was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Unclear
	Unclear how clinicians who enrolled the patients or assessing the outcomes, and the parents were blinded
Blinding of outcome assessment (detection bias)	Unclear
	Unclear how clinicians who enrolled the patients or assessing the outcomes, and the parents were blinded
Incomplete outcome data (attrition bias)	Low risk
	Reasons are reported and number of dropouts is balanced
Selective reporting (reporting bias)	High risk
	No protocol found, registration number leads to another study. In methods: "all of suspected adverse events were recorded", but only diarrhoea is reported as side effect in results.
Other bias	Unclear
	Baseline characteristics only reported for patients that made study end.

Savino 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Separate computer generated randomized lists were used for the 3 age groups.
Allocation concealment (selection bias)	Low
	Not reported. Contacted authors: central randomization by an external party
Blinding of participants and personnel (performance bias)	High risk
	Open label for patients. Only the doctor who performed evaluation was blinded.
Blinding of outcome assessment (detection bias)	High risk
	The doctor who performed the evaluation was not involved in the allocation of treatment and remained blinded as to the type of treatment received by patients during the study. However, most outcomes are patient reported and patients/parents were not blinded.
Incomplete outcome data (attrition bias)	Low risk
	Reasons are reported and number of dropouts is balanced
Selective reporting (reporting bias)	Low risk
	Protocol available. Key efficacy outcomes and safety outcomes reported as per protocol. However in results they have added 'adequate relief' as an outcome.
Other bias	Unclear
	Baseline characteristics are not reported for all randomized patients (patients who withdrew before receiving treatment are not described). Contacted authors: no data available.

Shahamat 2016	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Reported that only methodologist and statistician who assessed and analysed were blinded
Blinding of outcome assessment (detection bias)	High risk
	Reported that only methodologist and statistician who assessed and analysed were blinded
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline demographics balanced

Strisciuglio 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Predefined block randomisation list
Allocation concealment (selection bias)	Unclear
	Each centre opened the randomisation letters in sequential order, however unclear if letters were opaque and sealed
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	No reasons reported for the patients who dropped out immediately after randomisation, and not reported how many per group
Selective reporting (reporting bias)	Low risk
	Protocol available and followed. Efficacy and safety outcomes were reported as planned.
Other bias	High
	Baseline characteristics are not reported for all randomized patients (patients who withdrew immediately after randomisation are not described). After the initial 14 days of treatment, the participants received self-directed variable amounts of the agent, which could have affected the composition of the treatment groups.

Thomson 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	The random sequence group was computer generated before the start of recruitment using a block size of four patients
Allocation concealment (selection bias)	Low risk
	Randomisation numbers were sent to the investigator sites with number stored in sealed code-break envelopes.
Blinding of participants and personnel (performance bias)	Low risk
	Says who and how blinded and matched placebo was obtained.
Blinding of outcome assessment (detection bias)	Low risk
	Says who and how blinded and matched placebo was obtained.
Incomplete outcome data (attrition bias)	Unclear
	Unclear what "advanced straight to period III" means. Unclear if these patients were dropouts during period I.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Tavassoli 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomly allocated by the permuted randomisation method (with block sizes of four)
Allocation concealment (selection bias)	Low risk
	A random number list generated by using a computer was used to assign participants to two arms. The researcher conducting randomization was not involved in other parts of the study.
Blinding of participants and personnel (performance bias)	High risk
	Clinician was not blinded. Only containers were similar, nothing mentioned about taste and appearance.
Blinding of outcome assessment (detection bias)	High risk
	Clinician was not blinded. Only containers were similar, nothing mentioned about taste and appearance.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for dropout provided. Number of dropouts is balanced
Selective reporting (reporting bias)	Unclear
	The only efficacy outcome reported in the protocol was bowel frequency. In the study there were a lot more outcomes, unknown if these outcomes were predefined.
Other bias	Low risk
	Baseline characteristics balanced.

Treepongkaruna 2014	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomisation list of treatment allocation codes prepared by the contract research organisation responsible for operational management of the study.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Clear methods of how blinded and who (both patient and doctor)
Blinding of outcome assessment (detection bias)	Low risk
	Clear methods of how blinded and who (both patient and doctor)
Incomplete outcome data (attrition bias)	Low risk
	Reasons are reported and number of dropouts is balanced.
Selective reporting (reporting bias)	Low risk
	Protocol available. Safety outcomes not reported in protocol, but are reported in article.
Other bias	Low risk
	Baseline demographics balanced

Urganci 2005	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not reported how randomisation occurred
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear how many patients reached study end
Selective reporting (reporting bias)	High risk
	No protocol found and side effects were not adequately reported even though it was mentioned in the methods that side effects would be monitored.
Other bias	Low risk
	Baseline demographics balanced

Uhm 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not reported how randomisation occurred
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear how many patients reached study end
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Ustundag 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Randomization was performed by the use of sequential numbers allocated to the patients at the study entry.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	High risk
	No reasons for drop-out reported
Selective reporting (reporting bias)	High risk
	No protocol found. However, treatment success was given as outcome in methods, however no data reported in results.
Other bias	Unclear
	Baseline characteristics only reported for patients that made study end.

Voskuijl 2004	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Patients were randomly assigned to received either lactulose or PEG, not described how. Contacted authors: block randomisation
Allocation concealment (selection bias)	Low risk
	Unlabelled numbered boxes with unlabelled sachets were prepared by the AMC pharmacy and handed out to patients after randomisation.
Blinding of participants and personnel (performance bias)	High risk
	Says double blinded. Not clear who exactly and how both meds were identical (only both unlabelled, not taste and smell etc). Contacted authors: smell/taste etc was not the same. But difficult to make them identical.
Blinding of outcome assessment (detection bias)	High risk
	Says double blinded. Not clear who exactly and how both meds were identical (only both unlabelled, not taste and smell etc). Contacted authors: smell/taste etc was not the same. But difficult to make them identical.
Incomplete outcome data (attrition bias)	Low risk
	Reasons reported, numbers balanced. Both groups 1 patient 'reason unknown'
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Wang 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	The statistical software SAS was used to constructed random digit tables
Allocation concealment (selection bias)	Low risk
	Central allocation, children received drugs from drug administer. Packages were similar.
Blinding of participants and personnel (performance bias)	Unclear
	Same outer packaging and labels for the two drugs. Unclear if taste the same and if researchers were blinded (not reported)
Blinding of outcome assessment (detection bias)	Unclear
	Same outer packaging and labels for the two drugs. Unclear if taste the same and if researchers were blinded (not reported)
Incomplete outcome data (attrition bias)	Unclear
	No reason for drop out reported of 26 patients. Drop outs were equally divided. For the remaining drop outs the reasons were not reported per group.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Appendix 15. Risk of Bias beoordeling geïncludeerde artikelen niet-medicamenteuze behandeling

Abediny 2016*	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not reported how in the abstract
Allocation concealment (selection bias)	Unclear
	Not reported how in the abstract
Blinding of participants and personnel (performance bias)	High
	Single blinded. Parents not blinded.
Blinding of outcome assessment (detection bias)	High
	Single blinded. Parents not blinded.
Incomplete outcome data (attrition bias)	Unclear
	Not reported in the abstract
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Baseline demographics not reported in abstract

*Only abstract was in English. Not able to translate the full text.

Banaszkiewicz 2005	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	The allocation sequence and randomization list were computer-generated by investigators at the Medical University of Warsaw.
Allocation concealment (selection bias)	Unclear
	Allocation concealment was achieved by the use of study products with similar appearances and tastes, which were packed identically and which were indistinguishable from each other. Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment
Blinding of participants and personnel (performance bias)	Low risk
	Study products were packed identically and which were indistinguishable from each other. Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment
Blinding of outcome assessment (detection bias)	Low risk
	Study products were packed identically and which were indistinguishable from each other. Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment
Incomplete outcome data (attrition bias)	Low risk
	Drop outs reported, with reason. No imbalance between groups.
Selective reporting (reporting bias)	Unclear
	No protocol or trial registration found. Primary and secondary outcomes reported including statistical analysis plan.
Other bias	Low risk
	No baseline differences between groups

Basturk 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random but now how random occurred
Allocation concealment (selection bias)	Low risk
	Code numbers of drugs were unknown to doctor, nurse and patient. Only manufacturer knew.
Blinding of participants and personnel (performance bias)	Low risk
	Drugs that were completely same in colour, smell, taste, and packaging properties but had one of the two different code numbers on them were used. The ingredients of the drugs were unknown to the doctor, nurse, and the patient, and which code number included which ingredient was known to the manufacturer only.
Blinding of outcome assessment (detection bias)	Low risk
	Drugs that were completely same in colour, smell, taste, and packaging properties but had one of the two different code numbers on them were used. The ingredients of the drugs were unknown to the doctor, nurse, and the patient, and which code number included which ingredient was known to the manufacturer only.
Incomplete outcome data (attrition bias)	Unclear
	Drop outs reported, no reasons provided. No imbalance between groups.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration. Primary and secondary outcomes as reported in methods.
Other bias	Low risk
	No baseline differences between groups

Blanco-Diaz 2020	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated random sequence
Allocation concealment (selection bias)	Low risk
	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Unclear. Only report compliance and attendance rates. At every outcome measurement point, the number of patients differ. Unclear if patients were lost to follow-up.
Selective reporting (reporting bias)	High risk
	No protocol found. They do not mention anything about recording side effects during the study (only the Symptom Severity Score), but do say in their conclusion that Manual Therapy has no side effects.
Other bias	Low risk
	Baseline demographics balanced

Bongers 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer randomisation
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Formula cans were labelled with codes to mask identity of the study feedings. Neither the parent nor the physicians were aware of the composition of the formula until the entire study was completed. Taste was made the same for both.
Blinding of outcome assessment (detection bias)	Low risk
	Formula cans were labelled with codes to mask identity of the study feedings. Neither the parent nor the physicians were aware of the composition of the formula until the entire study was completed. Taste was made the same for both.
Incomplete outcome data (attrition bias)	Low risk
	Drop outs reported, reasons provided. No imbalance between groups.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration. Primary and secondary outcomes as reported in methods.
Other bias	Low risk
	No baseline differences between groups

Bourkheili 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer-generated randomisation code
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Only one drop out in CG, but no reason reported. Only one patient will not have big impact on the results.
Selective reporting (reporting bias)	High risk
	Protocol found. But primary outcome of the paper (treatment success) was not reported in protocol. Also no safety data reported, but in methods they do describe 'parents were advised to contact the therapist if their children experienced any signs and symptoms such as nausea, vomiting, diarrhoea, abdominal pain and skin symptoms.'
Other bias	Low risk
	Baseline demographics balanced. Do miss data of the one patient that was lost to follow up, but only one will not have big impact on the results.

Bu 2007	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer-generated randomization list
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Three interventions with similar appearances and placed into identical capsules.
Blinding of outcome assessment (detection bias)	Low risk
	Three interventions with similar appearances and placed into identical capsules
Incomplete outcome data (attrition bias)	Unclear
	Numbers per group reported, no imbalance. Reasons provided, however unclear which reasons belong to which patient/group. Two patients suffered from actue gastroenteritis, unclear in which group.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration.
Other bias	Low risk
	Baseline demographics balanced

Cai 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Low risk
	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk
	Double blinded. "We blinded the random result twice, named the drugs as drug A and drug B instead of the real name in the first level, and named the groups as group 1 and group 2 instead of treatment or placebo group in the second level. The second level could be unblinded for analysis, while the first level should be unblinded until trial summary."
Blinding of outcome assessment (detection bias)	Low risk
	Double blinded. "We blinded the random result twice, named the drugs as drug A and drug B instead of the real name in the first level, and named the groups as group 1 and group 2 instead of treatment or placebo group in the second level. The second level could be unblinded for analysis, while the first level should be unblinded until trial summary."
Incomplete outcome data (attrition bias)	Unclear
	Only reasons provided for the drop outs was: "Forty-eight cases in FAS (full analysis set) were excluded from the PPS (per protocol set) due to major protocol violations and poor medicine compliance" Dropout in herbal group: 34/360, dropout in placebo: 16/120. No imbalance, but no exact reasons provided and not per group/patient.
Selective reporting (reporting bias)	Unclear
	Protocol registered and key safety data and outcomes reported. However for their secondary efficacy results the number of patients are lower than the number of patients stated for either the FAS or PPS analysis. Unclear why the remaining patients were not included as they stated in their methods that "Efficiency measure data were analysed based on FAS and PPS".
Other bias	Low risk
	Baseline demographics balanced.

Canbulat 2017	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not reported
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High
	Not blinded
Blinding of outcome assessment (detection bias)	High
	Not blinded
Incomplete outcome data (attrition bias)	Low risk
	Drop outs reported, reasons provided. No imbalance between groups.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced.

Cassetari 2019	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Subjects were randomly assigned into five treatment groups by a mathematical algorithm
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Patients and personnel blinded. Biomass looked identical as a thick, white, homogenous mass. No substantial variation in colour, taste, and smell.
Blinding of outcome assessment (detection bias)	Low risk
	Patients and personnel blinded. Biomass looked identical as a thick, white, homogenous mass. No substantial variation in colour, taste, and smell.
Incomplete outcome data (attrition bias)	Low risk
	All drop outs per group reported with reasons.
Selective reporting (reporting bias)	Low risk
	Key outcomes and safety data reported per protocol.
Other bias	Low risk
	Baseline demographics balanced

Castilla 2021 (abstract only)	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Reported "simple random allocation", however unclear how randomisation occurred.
Allocation concealment (selection bias)	Unclear
	Not reported.
Blinding of participants and personnel (performance bias)	Unclear
	Not reported.
Blinding of outcome assessment (detection bias)	Unclear
	Not reported.
Incomplete outcome data (attrition bias)	Low risk
	All patients who were randomised, were included in the final analyses.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	No baseline characteristic data reported.

Chmielewska 2011	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomization, with a block size of 6, was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial.
Allocation concealment (selection bias)	Low risk
	The randomization sequence was concealed until all data were analysed. Study intervention products were prepared in sachets centrally by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the trial.
Blinding of participants and personnel (performance bias)	Unclear
	The active product and placebo were packaged in identical sachets and labelled with one of two codes. The appearance and texture of the dry products were identical. When mixed with water, the preparation of GNN turned into a substance of jelly-like consistency; however, this only happened if the solution was not consumed within a few minutes, which was the recommended time limit for consumption. Contact with authors confirmed that after mixing with water, the consistence of placebo was not like the one of glucomannan (if not consumed directly after preparation). The participants were not informed of the viscosity of the preparations.
Blinding of outcome assessment (detection bias)	Low risk
	Both the participants and researchers conducting the study, one of whom also performed data analysis, were blinded. packaging was identical, dry products were also identical.
Incomplete outcome data (attrition bias)	Low risk
	Flow chart. Drop outs reported with reasons. No imbalance between groups.
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety data and efficacy outcomes reported as per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Clarke 2009	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says randomised, but not reported how
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Unclear what the placebo treatment was and who were blinded. Treating physician could not be blinded, therefore high risk.
Blinding of outcome assessment (detection bias)	Unclear
	Unclear what the placebo treatment was and who were blinded. Patients were blinded.
Incomplete outcome data (attrition bias)	Low risk
	No drop outs
Selective reporting (reporting bias)	Unclear risk
	No protocol found
Other bias	Low risk
	Baseline demographics balanced.

Coccorullo 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Unclear
	Reported as double blind. Methods not mentioned, not clear who was blinded.
Blinding of outcome assessment (detection bias)	Unclear
	Reported as double blind. Methods not mentioned, not clear who was blinded.
Incomplete outcome data (attrition bias)	Low risk
	No drop outs reported.
Selective reporting (reporting bias)	Low risk
	Protocol. Key safety data and outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Croffie 2005	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says randomised, but not reported how
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	No mention of blinding in text or language akin to blinding.
Blinding of outcome assessment (detection bias)	High risk
	No mention of blinding in text or language akin to blinding.
Incomplete outcome data (attrition bias)	Low risk
	All drop outs reported with reasons.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced.

De Abreu 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomization was performed by shuffling blocks of 4 sealed, sequentially numbered brown envelopes.
Allocation concealment (selection bias)	Low risk
	Allocation was performed by independent research professional. Sealed opaque envelopes were used according to the randomization sequence.
Blinding of participants and personnel (performance bias)	High risk
	Sham PTNS. However, treating physician needed to know the group allocation, because the electrodes needed to be placed on the scapular (CG) region instead of sacral (IG). Treating physician was not part of rest of the study.
Blinding of outcome assessment (detection bias)	Low risk
	Parents, patients, and post-treatment evaluator were blinded to group allocation. Sham treatment. Researcher who carried out post-treatment evaluation was unaware of treatment allocation, some for data analysis.
Incomplete outcome data (attrition bias)	Low risk
	No imbalance, reason for dropout provided
Selective reporting (reporting bias)	High risk
	Protocol found. No safety data reported
Other bias	Low risk
	Baseline demographics balanced. See supplementary files.

Dehghani 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Patients and parents were not blinded, only paediatric gastroenterologist who evaluated the protocols at the end of treatment was blinded. Unclear if researcher was blinded.
Blinding of outcome assessment (detection bias)	High risk
	Patients and parents were not blinded, only paediatric gastroenterologist who evaluated the protocols at the end of treatment was blinded. Unclear if researcher was blinded.
Incomplete outcome data (attrition bias)	Low risk
	No drop outs reported.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details.
Other bias	Low risk
	Baseline demographics balanced.

Dehghani 2019	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Low risk
	Word 'allocation' used to describe joining group without further discussion. Contacted author, answer: allocation concealment was done by numbered drug containers.
Blinding of participants and personnel (performance bias)	Low risk
	Drug and placebo prepared with similar organoleptic properties; packaged in identical containers. Patients and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk
	Drug and placebo prepared with similar organoleptic properties; packaged in identical containers. Patients and personnel blinded.
Incomplete outcome data (attrition bias)	Low risk
	Flow of patients including randomised and assessed, drop outs reported with reasons given in flow chart.
Selective reporting (reporting bias)	Low risk
	Key outcomes and safety data reported per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Engelenburg 2017	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Unclear risk
	Not clear if allocation was concealed.
Blinding of participants and personnel (performance bias)	High risk
	Open label. Practitioners and patients were not blinded (not possible).
Blinding of outcome assessment (detection bias)	High risk
	Open label. Practitioners and patients were not blinded (not possible). Study used patient reported outcomes. Outcome assessor was blinded and independent.
Incomplete outcome data (attrition bias)	Low risk
	Flow chart. Drop outs reported with reasons.
Selective reporting (reporting bias)	Low
	Trial registration numbers reported and protocol found. Primary outcome reported as per protocol.
Other bias	Low risk
	Baseline demographics balanced.

Esmaeilidooki 2016	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Stated 'Simple Randomisation' without specified method.
Allocation concealment (selection bias)	Unclear
	Stated 'Random allocation' without specified method.
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety data and outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Fabrizio 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated randomization
Allocation concealment (selection bias)	Low risk
	Intervention schedules were provided in sealed envelopes for each study site. Study formula was assigned by opening the next sequential envelope at the study site.
Blinding of participants and personnel (performance bias)	Low risk
	Study formulas, each designated by two unique codes known only to the sponsor, were dispensed to parents at randomization. Neither the product labels nor the sealed envelopes allowed direct unblinding by the study site. Personnel responsible for monitoring the study were also blinded to study product identification.
Blinding of outcome assessment (detection bias)	Low risk
	Study formulas, each designated by two unique codes known only to the sponsor, were dispensed to parents at randomization. Neither the product labels nor the sealed envelopes allowed direct unblinding by the study site. Personnel responsible for monitoring the study were also blinded to study product identification.
Incomplete outcome data (attrition bias)	Unclear
	No imbalance, but Reasons for drop out unclear. Ask authors.
Selective reporting (reporting bias)	Unclear
	No protocol found. Key outcomes reported as described in methods.
Other bias	Low risk
	Baseline demographics balanced

Gan 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not reported
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Single blinded. Assume only the patients were blinded, placebo controlled. No mention of how and who blinded and if placebo was matched.
Blinding of outcome assessment (detection bias)	High risk
	Single blinded. Assume only the patients were blinded, placebo controlled. No mention of how and who blinded and if placebo was matched.
Incomplete outcome data (attrition bias)	Unclear
	Unclear why patients 'incorrectly enrolled' and if they had already received treatment or not, in results section they say 'incomplete data'.
Selective reporting (reporting bias)	Low risk
	Trial registration number reported. They do report trial was registered at clinicaltrials.gov. That is not correct. Instead it is registered at Chinese trial registry. Outcomes match protocol.
Other bias	Low risk
	Baseline demographics balanced.

Guerra 2011	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Unclear
	Allocation sequence computer generated, but unclear if allocation was concealed.
Blinding of participants and personnel (performance bias)	Low risk
	The two products, goat yogurt with or without B. longum were identical in weight, colour, smell, taste and package. All doctors and children involved were unaware of the treatment administered.
Blinding of outcome assessment (detection bias)	Low risk
	The two products, goat yogurt with or without B. longum were identical in weight, colour, smell, taste and package. All doctors and children involved were unaware of the treatment administered.
Incomplete outcome data (attrition bias)	Low risk
	Only 1 withdrawal in the control group, no reason provided. But only 1, so not expected to have impacted the results.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details.
Other bias	Low risk
	Baseline demographics balanced.

Iacono 1998	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated
Allocation concealment (selection bias)	Low risk
	The milk was supplied in bottles coded A or B by the hospital dispensary
Blinding of participants and personnel (performance bias)	Unclear
	Says double blinded, but unclear how both treatments were matched. Only that the bottles were coded A or B. Not if taste, smell etc were matched. Researchers were unaware of treatment assignment.
Blinding of outcome assessment (detection bias)	Unclear
	Says double blinded, but unclear how both treatments were matched. Only that the bottles were coded A or B. Not if taste, smell etc were matched. Researchers were unaware of treatment assignment.
Incomplete outcome data (attrition bias)	Low risk
	No dropouts
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Data reported for all patients (cross-over study). Therefore unclear how baseline characteristics were divided between the two groups.

Imanieh 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Permuted block randomization was used for randomly allocating the participants to the two groups.
Allocation concealment (selection bias)	Low risk
	Allocation concealment was achieved using the dark envelope method.
Blinding of participants and personnel (performance bias)	Low risk
	Containers with the same shape, colour, and weight, so that the containers and solutions would not be distinguishable (no mention of taste). The patients, physicians, and the analyst were not aware of the ingredients of the solutions, only the pharmacist.
Blinding of outcome assessment (detection bias)	Low risk
	Containers with the same shape, colour, and weight, so that the containers and solutions would not be distinguishable (no mention of taste). The patients, physicians, and the analyst were not aware of the ingredients of the solutions, only the pharmacist
Incomplete outcome data (attrition bias)	Low risk
	Reasons provided. No imbalance in number of patients per group (6 vs 2)
Selective reporting (reporting bias)	Unclear
	Primary outcome in paper: not fulfilling Rome IV criteria anymore. In protocol primary outcomes are all Rome IV criteria (and more) separately.
Other bias	High risk
	Most of the baseline demographics balanced. Duration of functional constipation differs between groups: 74% of IG and 44% CG had been suffering from functional constipation for more than 12 months.

Jadresin 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Random allocation software
Allocation concealment (selection bias)	Low risk
	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk
	Both interventions were of the same taste, colour, smell, identical packaging, produced by producer not involved with the rest of the study. All study personnel, parents and guardians were unaware of the group assignments
Blinding of outcome assessment (detection bias)	Low risk
	Both interventions were of the same taste, colour, smell, identical packaging, produced by producer not involved with the rest of the study. All study personnel, parents and guardians were unaware of the group assignments
Incomplete outcome data (attrition bias)	Low risk
	Drop outs reported, with reason. No imbalance.
Selective reporting (reporting bias)	High risk
	Protocol is for both functional abdominal pain and FC. Paper only reports FC patients. Primary outcomes in protocol do not match primary outcomes in paper.
Other bias	Unclear
	No difference between age and gender between IG and CG. However, age and gender were the only baseline characteristics that were provided. More information needed.

Khan 2020	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Random number spreadsheet
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Not reported
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details.
Other bias	Unclear
	Baseline demographics not reported per group, but for whole cohort.

Khodadad 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Randomisation was generated by their biostatistics consultant. However, unclear how randomisation occurred.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Unclear
	Physicians and nurses were blinded. Bottles and sachets were similar in shape, taste and colour. Only label indicating A or B. However: Group A received 1.5 ml/kg/day oral liquid paraffin plus placebo, group B received 1 sachet synbiotic per day, Group C received 1.5 ml/kg/day oral liquid paraffin and 1 sachet synbiotic per day. Group B seemed to only receive a sachet with synbiotics, no placebo for laxative.
Blinding of outcome assessment (detection bias)	Unclear
	Physicians and nurses were blinded. Bottles and sachets were similar in shape, taste and colour. Only label indicating A or B. However: Group A received 1.5 ml/kg/day oral liquid paraffin plus placebo, group B received 1 sachet synbiotic per day, Group C received 1.5 ml/kg/day oral liquid paraffin and 1 sachet synbiotic per day. Group B seemed to only receive a sachet with synbiotics, no placebo for laxative.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart with reasons.
Selective reporting (reporting bias)	Low risk
	Key outcomes (efficacy and safety) reported as per protocol
Other bias	Low risk
	Baseline characteristics balanced

Kokke 2008	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Use of sequential numbers allocated to the patients at study entry and coordinated by the logistics manager of Numico Research using a block design.
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk
	Clear description of how both interventions were packed and prepared. Products could not be distinguished.
Blinding of outcome assessment (detection bias)	Low risk
	Clear description of how both interventions were packed and prepared. Products could not be distinguished.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart
Selective reporting (reporting bias)	Unclear
	No protocol
Other bias	Unclear
	Baseline characteristics reported for patients who reached end of study.

Kubota 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk
	All caregivers, patients, research staff, and physicians were blinded to which treatment group the patients belonged. Identical matching placebo and probiotic. bottles were matched and taste/texture were matched.
Blinding of outcome assessment (detection bias)	Low risk
	All caregivers, patients, research staff, and physicians were blinded to which treatment group the patients belonged. Identical matching placebo and probiotic. bottles were matched and taste/texture were matched.
Incomplete outcome data (attrition bias)	Unclear
	Unclear to which group the excluded patients belonged to. Only 3 patients.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Ladi-Seyedian 2020	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	No dropouts
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Lee 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomization was implemented automatically using Random Allocation Software 2.0 (Informer Technologies, Inc, Dallas, TX, USA) with a random block size
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	High risk
	High amount of drop-outs, imbalance > 20% and reasons not specified for each group
Selective reporting (reporting bias)	Low risk
	Protocol found. Key outcomes reported as per protocol. Safety data also reported in study.
Other bias	Low risk
	"There were no differences in age, disease duration, or other clinical characteristics among the 3 groups." There were sex differences between combination therapy and s. boulardii. They adjusted for sex in their Cox Regression analysis.

Loening-Baucke 1990	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Sealed envelopes with 4x4-inch cards indicating either conventional therapy alone or conventional therapy with biofeedback training were used for randomization. More information is needed.
Allocation concealment (selection bias)	Low risk
	Sealed envelopes
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Drop outs reported with reason, no imbalance.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced. There were more girls in biofeedback group compared to conventional (9/22 vs 1/19), but treatment success between boys and girls did not differ in the biofeedback group. For standard treatment sex has not a big impact.

Loening-Baucke 2004	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Only reported that patients were randomised by envelope. More information is needed.
Allocation concealment (selection bias)	Unclear
	With envelopes, but not mentioned whether the envelopes were sealed or not.
Blinding of participants and personnel (performance bias)	Unclear
	Says double blinded, but unclear who exactly were blinded. Both treatments had similar capsules, but unsure about same taste etc.
Blinding of outcome assessment (detection bias)	Unclear
	Says double blinded, but unclear who exactly were blinded. Both treatments had similar capsules, but unsure about same taste etc.
Incomplete outcome data (attrition bias)	Unclear
	Drop outs reported without reason, no imbalance (6 vs 7)
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Lojanatorn 2023	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	A computer generated list
Allocation concealment (selection bias)	Low risk
	Allocation was performed by an independent pharmacy
Blinding of participants and personnel (performance bias)	High risk
	Could not create identical containers (see discussion)
Blinding of outcome assessment (detection bias)	High risk
	Could not create identical containers (see discussion)
Incomplete outcome data (attrition bias)	Low risk
	No imbalance >20% and reason of dropout provided
Selective reporting (reporting bias)	Unclear
	States that trial registration is published retrospectively. Trial registered retrospectively (at 19 February 2021 and first recruitment 1 February 2021).
Other bias	Low risk
	Baseline demographics balanced

Mao 2015	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random, but not how random occurred
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	As Above
Incomplete outcome data (attrition bias)	Unclear
	Not reported
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Mozaffarpur 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Systematic randomisation
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Low risk
	Key outcomes (efficacy and safety) reported as per protocol
Other bias	Low risk
	Baseline characteristics balanced

Nasri 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not clear how patients were randomly assigned
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	No drop outs reported.
Selective reporting (reporting bias)	High risk
	Protocol available. However, safety data not reported, was described in protocol as a secondary outcome + in methods section.
Other bias	Low risk
	Baseline demographics balanced

Nimrouzi 2015	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomization
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Reasons per group reported. No imbalance per group.
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Unclear
	Baseline characteristics not reported for all included patients, only the ones that reached study end.

Olgac 2013	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random, but not how random occurred
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Qiao 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	According to the sequence generated by Random Allocation Software (version 1.0.0), the grouping was randomized in a ratio of 1:1, which was performed by a nonrecruited researcher
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	The placebo group received a placebo designed to match the CHM group based on appearance, weight, colour, taste, and odour, including 5% drug ingredients and 95% dextrin. Randomisation was performed by a nonrecruited researcher. Patients, researchers, evaluators, and sponsors did not know which patients received which treatments.
Blinding of outcome assessment (detection bias)	Low risk
	The placebo group received a placebo designed to match the CHM group based on appearance, weight, colour, taste, and odour, including 5% drug ingredients and 95% dextrin. Randomisation was performed by a nonrecruited researcher. Patients, researchers, evaluators, and sponsors did not know which patients received which treatments.
Incomplete outcome data (attrition bias)	Low risk
	No imbalance. Reasons provided for dropouts
Selective reporting (reporting bias)	Unclear
	Unclear defined outcomes: full remission and improvement were predefined, however in the results they use recovery rate. Unclear what recovery rate refers to. Protocol found, seems to meet protocol.
Other bias	Low risk
	Baseline demographics balanced

Quitadamo 2012	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomly assigned according to an automatically generated randomization list
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Clear reasons for drop-out per patient. Difference between both groups > 20%, but this is a result of the difference in drug (bad taste).
Selective reporting (reporting bias)	Unclear
	No protocol found
Other bias	Low risk
	Baseline demographics balanced

Reeves 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation protocol.
Allocation concealment (selection bias)	High risk
	Not concealed random list. Clinicians would conduct their visit with the patient, diagnose functional constipation, and offer enrolment on the study. They would review the block randomization figure and see which treatment was next (IG or CG).
Blinding of participants and personnel (performance bias)	High risk
	Could not be blinded.
Blinding of outcome assessment (detection bias)	High risk
	Could not be blinded.
Incomplete outcome data (attrition bias)	Unclear
	Unclear how many per group. No randomized numbers per group. No reasons provided.
Selective reporting (reporting bias)	Low risk
	Key outcome measurements reported as per protocol. Rest of the study also as per protocol.
Other bias	Unclear
	Baseline demographics not provided of all patients who were randomized.

Russo 2017	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Automatically generated randomization
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open Label Trial
Blinding of outcome assessment (detection bias)	High risk
	Open Label Trial
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline demographics balanced.

Sadeghzadeh 2014	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random, but not how random occurred
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Unclear
	Says double blinded, but unclear who exactly were blinded. Both treatments had similar sachets, but nothing mentioned if taste, colour etc or similar.
Blinding of outcome assessment (detection bias)	Unclear
	Says double blinded, but unclear who exactly were blinded. Both treatments had similar sachets, but nothing mentioned if taste, colour etc or similar.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Unclear
	Baseline characteristics not reported for all included patients, only the ones that reached study end. Only age and gender reported.

Saneian 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomization was done with a computer-generated random number list prepared by an investigator with no clinical involvement in the trial.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Unclear
	Unclear how clinicians who enrolled the patients or assessing the outcomes, and the parents were blinded
Blinding of outcome assessment (detection bias)	Unclear
	Unclear how clinicians who enrolled the patients or assessing the outcomes, and the parents were blinded
Incomplete outcome data (attrition bias)	Low risk
	Reasons are reported and number of dropouts is balanced
Selective reporting (reporting bias)	High risk
	No protocol found, registration number leads to another study. In methods: "all of suspected adverse events were recorded", but only diarrhoea is reported as side effect in results.
Other bias	Unclear
	Baseline characteristics only reported for patients that made study end.

Savino 2005	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random, but not how randomisation occurred
Allocation concealment (selection bias)	Low risk
	Randomised to IG/CG via sealed envelopes
Blinding of participants and personnel (performance bias)	High risk
	Not mentioned - assumed to be open label. No conceivable way to blind.
Blinding of outcome assessment (detection bias)	High risk
	Not mentioned - assumed to be open label. No conceivable way to blind.
Incomplete outcome data (attrition bias)	Unclear
	Drop-outs reported without reasons given, no imbalance.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline demographics balanced.

Sevilla 2022	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated randomization sequence in blocks of 10
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Low risk
	Two dropouts in IG, reasons not reported. Not expected to have an impact on results.
Selective reporting (reporting bias)	Low risk
	Critical outcomes reported. Protocol found, outcomes reported as per protocol.
Other bias	Low risk
	Baseline demographics balanced

Shahamat 2016	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Reported that only methodologist and statistician who assessed and analysed were blinded
Blinding of outcome assessment (detection bias)	High risk
	Reported that only methodologist and statistician who assessed and analysed were blinded
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline demographics balanced

Sharifi-Rad 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation
Allocation concealment (selection bias)	Low risk
	Computer-generated list of random numbers was used to allocate participants
Blinding of participants and personnel (performance bias)	High risk
	Patients, parents and physicians blind as well as outcome assessors. Physiotherapists were not.
Blinding of outcome assessment (detection bias)	Low risk
	As Above
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flowchart with reasons.
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Silva 2013	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Table of randomised numbers created by individual external to study to determine random distribution sequence of patients
Allocation concealment (selection bias)	Unclear
	The information remained the exclusive knowledge of one research assistant, who used these numbers to allocate patients by order of study entry immediately after receiving informed consent, and was made known to the researchers only after the statistical analysis. Need to know if research assistant is involved or not.
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Says analysis of the two groups at the end of the follow-up period for primary and secondary outcome measures was blind, but not reported how.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline demographics balanced.

Souza 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Computer generated random number table
Allocation concealment (selection bias)	Unclear
	Says assigned to blocks. Unclear how.
Blinding of participants and personnel (performance bias)	Low risk
	Double blind. Identical packaging and coding standardised. Reported
Blinding of outcome assessment (detection bias)	Low risk
	Double blind. Identical packaging and coding standardised. Reported
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flowchart with reasons.
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Sunic 2002	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random but no rationale or method given
Allocation concealment (selection bias)	Unclear
	Says allocated but no rationale or method given
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Not reported
Selective reporting (reporting bias)	High risk
	No protocol found. No safety outcomes reported.
Other bias	Low risk
	Baseline demographics balanced.

Tabbers 2011	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Block randomisation performed by Danone Research prior to the study onset
Allocation concealment (selection bias)	Low risk
	Central allocation.
Blinding of participants and personnel (performance bias)	Low risk
	The two treatments were identical in weight, colour, smell, taste and package. All doctors, research staff and patients involved are unaware of the treatment administered to the patient.
Blinding of outcome assessment (detection bias)	Low risk
	The two treatments were identical in weight, colour, smell, taste and package. All doctors, research staff and patients involved are unaware of the treatment administered to the patient.
Incomplete outcome data (attrition bias)	Low risk
	5/79 in IG dropped out with reason 'lost to follow up' and 6/80 in CG. For other drop outs (6 in IG and 4 in CG) reasons were provided.
Selective reporting (reporting bias)	Low risk
	Protocol published as separate articles. Key outcomes reported as per protocol (safety and efficacy)
Other bias	Low risk
	Baseline characteristics balanced

Tavassoli 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomly allocated by the permuted randomisation method (with block sizes of four)
Allocation concealment (selection bias)	Low risk
	A random number list generated by using a computer was used to assign participants to two arms. The researcher conducting randomization was not involved in other parts of the study.
Blinding of participants and personnel (performance bias)	High risk
	Clinician was not blinded. Only containers were similar, nothing mentioned about taste and appearance.
Blinding of outcome assessment (detection bias)	High risk
	Clinician was not blinded. Only containers were similar, nothing mentioned about taste and appearance.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for dropout provided. Number of dropouts is balanced
Selective reporting (reporting bias)	Unclear
	The only efficacy outcome reported in the protocol was bowel frequency. In the study there were a lot more outcomes, unknown if these outcomes were predefined.
Other bias	Low risk
	Baseline characteristics balanced.

Tjokronegoro 2020	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	The randomization list was established with a permutation block of constant length (6 subjects per block).
Allocation concealment (selection bias)	Low risk
	The list was placed in a concealed envelope and was stored until the end of study.
Blinding of participants and personnel (performance bias)	Low risk
	The probiotics and placebo were manufactured by Novell Pharmaceutical Laboratories as identical powder with similar appearance and taste, which were packed in identical aluminium sachets. Throughout the study, investigator, participants, and data analyst were blinded to the assigned treatment.
Blinding of outcome assessment (detection bias)	Low risk
	The probiotics and placebo were manufactured by Novell Pharmaceutical Laboratories as identical powder with similar appearance and taste, which were packed in identical aluminium sachets. Throughout the study, investigator, participants, and data analyst were blinded to the assigned treatment.
Incomplete outcome data (attrition bias)	Low risk
	In balance. Almost all reasons provided. Only of 1 patient no reason provided for drop out.
Selective reporting (reporting bias)	Unclear
	Protocol not found
Other bias	Low risk
	Baseline demographics balanced

Ustundag 2010	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Randomization was performed by the use of sequential numbers allocated to the patients at the study entry.
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	High risk
	No reasons for drop-out reported
Selective reporting (reporting bias)	High risk
	No protocol found. However, treatment success was given as outcome in methods, however no data reported in results.
Other bias	Unclear
	Baseline characteristics only reported for patients that made study end.

Van der Plas 1996	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Says random but no rationale or method given
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open label. But could not be blinded.
Blinding of outcome assessment (detection bias)	High risk
	Open label. But could not be blinded.
Incomplete outcome data (attrition bias)	Low risk
	Reasons for drop-out are clear and no imbalance
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Van Dijk 2008	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	A computer-based system was used to generate a sequence of random group assignment for consecutive patients.
Allocation concealment (selection bias)	Low risk
	A research assistant performed a telephone call to a randomization centre and revealed the allocation to parents immediately.
Blinding of participants and personnel (performance bias)	High risk
	Open label. But could not be blinded.
Blinding of outcome assessment (detection bias)	High risk
	Open label. But could not be blinded.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flowchart with reasons.
Selective reporting (reporting bias)	Low risk
	Protocol. Key safety outcomes reported.
Other bias	Low risk
	Baseline characteristics balanced

Weber 2014	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Random number table
Allocation concealment (selection bias)	Unclear
	Says assigned to 1:1 blocks, unclear how allocation happened.
Blinding of participants and personnel (performance bias)	Low risk
	Double blinded. Patients and parents blinded. Both IG and CG labelling was standardised, products resembles each other and administered in an identical manner.
Blinding of outcome assessment (detection bias)	Low risk
	Double blinded. Patients and parents blinded. Both IG and CG labelling was standardised, products resembles each other and administered in an identical manner.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart with reasons.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Low risk
	Baseline characteristics balanced

Wegner 2018	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Randomly assigned according to automatically generated randomisation list
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	Unclear
	States double blind but only States "matching placebo and macrogol". More information needed if and how personnel was blinded.
Blinding of outcome assessment (detection bias)	Unclear
	States double blind but only States "matching placebo and macrogol". More information needed if and how personnel was blinded.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart with reasons.
Selective reporting (reporting bias)	Low risk
	Protocol and NCT registration present in article. Safety and primary outcome reported per protocol
Other bias	Low risk
	Baseline characteristics balanced

Wojtyniak 2017	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	The randomization list was generated by an investigator with no clinical involvement in the trial, via a computer program (StatsDirect) with an allocation ratio of 1:1 and with a block of 6
Allocation concealment (selection bias)	Low risk
	The allocation sequence was concealed from the researchers responsible for enrolling and assessing participants in sequentially numbered, white, opaque, sealed, and stapled envelope.
Blinding of participants and personnel (performance bias)	Low risk
	Identical capsules with an identical taste, smell, and appearance.
Blinding of outcome assessment (detection bias)	Low risk
	Identical capsules with an identical taste, smell, and appearance.
Incomplete outcome data (attrition bias)	Low risk
	All drop-outs reported per group as represented in flow chart with reasons - provided in appendix at article end
Selective reporting (reporting bias)	Low risk
	Protocol available. Key safety outcomes reported.
Other bias	Low risk
	Baseline characteristics balanced

Xu 2015	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Unclear how children were randomised exactly
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	High risk
	Open-label. Unable to do blinded trial.
Blinding of outcome assessment (detection bias)	High risk
	Open-label. Unable to do blinded trial.
Incomplete outcome data (attrition bias)	Unclear
	Not reported.
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Unclear
	Not reported

Young 1998	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Unclear
	Not mentioned
Allocation concealment (selection bias)	Unclear
	Not mentioned
Blinding of participants and personnel (performance bias)	High risk
	Open label
Blinding of outcome assessment (detection bias)	High risk
	Open label
Incomplete outcome data (attrition bias)	Unclear
	Not reported
Selective reporting (reporting bias)	Unclear
	No protocol found or trial registration details
Other bias	Unclear
	Not reported per group

Yu 2023	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Sequence generated by Random Allocation Software (version 1.0.0), the grouping was randomized in a 1:1 ratio
Allocation concealment (selection bias)	Low risk
	Asked author: Central allocation
Blinding of participants and personnel (performance bias)	High risk
	Patients with different treatments were assigned to different rooms or different periods to prevent communication between patients. The treatment process was completed by nurses and they did not participate in the collection and evaluation of results. Evaluators did not participate in the treatment process. Control group received a sham PTNS. But treating nurse cannot have ben blinded for intervention. Also unclear what how sham was exactly performed.
Blinding of outcome assessment (detection bias)	Low risk
	Patients with different treatments were assigned to different rooms or different periods to prevent communication between patients. The treatment process was completed by nurses and they did not participate in the collection and evaluation of results. Evaluators did not participate in the treatment process. Control group received a sham PTNS.
Incomplete outcome data (attrition bias)	Low risk
	In balance. Only of two drop outs no reason provided (out of total of 9)
Selective reporting (reporting bias)	Low risk
	Key outcomes reported as per protocol. Safety not reported in protocol, but reported in paper (methods and results)
Other bias	Low risk
	Baseline demographics balanced

Zaja 2021	
Bias	**Authors' judgement and support for judgement**
Random sequence generation (selection bias)	Low risk
	Automatically generated randomisation list
Allocation concealment (selection bias)	Unclear
	Not reported
Blinding of participants and personnel (performance bias)	Low risk
	Group-2 received placebo, consisting of an identical formulation in all aspects, except excluded the live bacteria. The study personnel, healthcare providers, patients and parents were blinded to the study group allocation.
Blinding of outcome assessment (detection bias)	Low risk
	Group-2 received placebo, consisting of an identical formulation in all aspects, except excluded the live bacteria. The study personnel, healthcare providers, patients and parents were blinded to the study group allocation.
Incomplete outcome data (attrition bias)	Low risk
	No dropouts.
Selective reporting (reporting bias)	Low risk
	Protocol found. Outcomes reported as per protocol.
Other bias	Low risk
	Baseline demographics balanced