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[Intervention Protocol]

Treatments for intractable constipation in childhood

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the efficacy and safety of treatments used for intractable constipation in children.

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BACKGROUND

Description of the condition

Constipation is one of the most common reasons for referrals to paediatricians, accounting for approximately 3-5% of general paediatric consultations, with the vast majority of those being for chronic constipation without a physical aetiology, known as functional constipation (Philichi 2018). Depending on the criteria used for diagnosis, 1 out of 100 children and young people have idiopathic constipation in the UK, and the estimated worldwide prevalence ranges from 3% to 30% (NICE 2013; Waterham 2017). Epidemiological data suggest constipation is becoming increasingly prevalent in South America, Asia, and Europe (Rajindrajith 2016).

Constipation, as a clinical entity, can range from mild disease, which responds to maintenance laxative drug treatment, to severe disease, which requires aggressive and invasive treatments. The Rome criteria, currently in its fourth iteration, is a clinically useful tool for defining functional constipation in children, and is recognised as the reference standard criteria in most major international clinical guidelines (Schmulson 2017).

A universal case definition of intractable constipation remains elusive, but is broadly defined as constipation that does not respond to conventional medical therapy (NICE 2013; Tabbers 2014). The specific transition point between chronic constipation and intractable constipation is not clear. It is also poorly defined in terms of symptom duration, and the specific components of 'intensive or maximal medical therapy'. Regardless of the case definition used to define intractable constipation, the impact of constipation on the child and their caregivers is universally recognised (Rajindrajith 2016; Rajindrajith 2020). Unresolved constipation can negatively impact health-related quality of life indicators, with additional implications for providing healthcare systems. The annual medical costs of children with constipation are approximately twice as much as in children who do not suffer from constipation, reflecting increased outpatient and emergency department visits in the constipated child (Shah 2011).

A significant factor that complicates recommendations for this condition is that there is a disarray of definitions for intractable constipation. For example, the National Institute of Health and Care Excellence (NICE) defines intractable constipation as that which does not respond to sustained, optimum medical management, but fails to comment on the duration of symptoms or the therapeutic pathways (NICE 2013). On the other hand, the guidelines jointly published by the North American and European Societies of Paediatric Gastroenterology (NASPGHAN and ESPGHAN) define intractable constipation as that which does not respond to optimum medical treatment for at least three months (Tabbers 2014).

Description of the intervention

While a small number of important organic diseases are associated with constipation, including Hirschsprung's disease, celiac disease, intestinal neuronal dysplasia, and hypothyroidism, the majority of infantile and childhood constipation is thought to be functional in aetiology (Youssef 2001). In the absence of an organic aetiology underpinning constipation, treatment aims to mitigate against a range of contributory factors (e.g. pain, poor fluid intake, and psychological barriers), often necessitating a multidisciplinary approach (NICE 2013). From a therapeutic perspective, laxative therapy represents the mainstay medical therapy, and is used alongside adjuvant therapies, such as dietary and behavioural modification (Gordon 2016). Osmotic laxatives, such as lactulose and polyethylene glycol (PEG), are valuable agents, since they can be administered easily to young children in the form of a solution (Gordon 2016). Stimulant laxatives, for which senna and bisacodyl feature commonly in disimpaction regimens, are available in various forms, including tablets, liquids, and suppositories (Portalatin 2012; Southwell 2020a; Vriesman 2020a).

How the intervention might work

Regardless of the specific intervention, the aim of treatment is to achieve complete disimpaction with minimal discomfort. The diverse range of available interventions reflects the complexity of this challenging condition. Laxative therapy, regardless of whether it is delivered orally, as a suppository, or via an antegrade continent enema, aims to relieve constipation by either increasing the water content of stool, making stools softer, or stimulating peristaltic action. As an acetylcholinesterase inhibitor, botulinum toxin exerts its effects by causing clinically reversible muscle paralysis (Irani 2008; Ahmadi 2013). The mechanisms underpinning colonic trans-anal irrigation, include simple mechanical washout, and stimulation of peristalsis (Emmett 2015). In principle, transcutaneous electrical stimulation (TES) generates an electrical impulse that acts as a stimulus for appropriate peripheral nerves (Ng 2016). Other theories postulated are that TES acts centrally, and re-balances excitatory and inhibitory signals, resulting in the normalisation of the neural drive (Sluka 2003). Colonic resection, with anastomosis or bowel diverting stoma, is thought to be effective by eliminating a dysfunctional mega-rectum (Siminas 2015).

Why it is important to do this review

The most severe cases of intractable constipation may necessitate the most invasive of therapies, such as bowel resection, antegrade enemas, and the use of neuromodulation. Since many of these interventions are invasive, and in some cases, irreversible, it is crucial to identify which interventions are the most effective, and in which clearly defined groups of people with constipation. Furthermore, there are potential adverse effects associated with all the treatments described. For instance, laxative therapy can cause abdominal discomfort and excessive flatulence (McClung 2004). While widely considered a safe treatment, trans-anal irrigation can cause bowel perforation and chemical colitis (Emmanuel 2010). The antegrade continence enema (ACE) procedure is associated with peritonitis, stomal stenosis, and stomal leak, in addition to high rates of relapse (Siddiqui 2014; Chan 2016). Given the risks associated with the spectrum of treatments available for children with intractable constipation, it is important to determine the efficacy of such treatments, in addition to evaluating their safety profiles.

There are a number of Cochrane Reviews within the context of paediatric constipation, such as the comparison between osmotic and stimulant laxatives for childhood constipation (Gordon 2016), and probiotics for treating chronic childhood constipation (Gordon 2016a), but there is no review for paediatric disease that is considered intractable in severity. Therefore, there is an urgent need to identify the most efficacious management

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strategies for children with intractable constipation, to reduce the burden of morbidity, and long-term sequelae of refractory disease (Southwell 2020a). This review will be of interest to frontline clinicians, commissioning groups, and those involved in developing guidelines and policy.

OBJECTIVES

To evaluate the efficacy and safety of treatments used for intractable constipation in children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all types of randomised controlled trials (RCTs), including cross-over and cluster RCTs.

Types of participants

We will include trials with children from birth to 18 years of age, with a diagnosis of intractable functional constipation, with or without incontinence. We will use this case definition of intractable functional constipation: constipation that has not responded to conventional medical therapy (as defined by the individual studies).

Types of interventions

We will include studies that compare any treatment or intervention for intractable constipation to either another intervention or treatment, or placebo.

Eligible treatments and interventions include, but are not limited to:

- any pharmacological therapy intended to treat constipation (osmotic laxative, stimulant laxative, bulking agent, faecal softeners, cholinergic agents) administered either orally, rectally, or via an antegrade continent enema
- botulinum toxin injection
- colonic trans-anal irrigation
- transcutaneous electric stimulation
- acupuncture
- pelvic floor physiotherapy
- definitive surgical interventions (e.g. bowel resection with colostomy)

Types of outcome measures

The outcome measures used in this review will reflect the recommendations of the Rome foundation paediatric sub-committee on clinical trials (Koppen 2018a).

Primary outcomes

1. Non-fulfilment of the Rome IV criteria for functional constipation, measured at the end of the study period
2. The frequency of defecation (number of stools per week), measured at the end of the study period
3. Treatment success (as defined by the primary study)
4. Adverse events (as defined by the primary study)

Secondary outcomes

1. Stool consistency (measured using a validated scale)
2. Painful defecation (measured using a validated scale)
3. Quality of life (as defined by the primary study)
4. Faecal incontinence frequency
5. Abdominal pain (measured using a validated scale)
6. Admission to hospital for disimpaction
7. School absence

Search methods for identification of studies

We will use the following methods to identify studies for inclusion.

Electronic searches

We will conduct a computer-assisted search for relevant studies (from database inception).

- Cochrane Central Register of Controlled Trials ((CENTRAL via Ovid Evidence-Based Medicine Reviews Database (EBMR); Appendix 1);
- MEDLINE Ovid (from 1946; Appendix 2);
- Embase Ovid (from 1974; Appendix 3);

We will search the following trial registries by combining terms related to intractable and constipation in Children.

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/).

We will not impose any date or language restrictions on the searches. Studies published in a non-English language will be professionally translated in full.

Searching other resources

The references of all identified studies will be inspected for additional randomised trials potentially eligible for inclusion.

Data collection and analysis

We will carry out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Selection of studies

Two reviewers will independently screen titles, abstracts, and full reports for eligibility against the inclusion criteria.

The two review authors will identify reports that appear to be potentially relevant. We will obtain the full-text reports of those that appear to be potentially relevant. After reading the full texts, the two review authors will independently assess the eligibility of trials, based on the inclusion criteria and develop a PRISMA flowchart (Page 2021).

Data extraction and management

We will develop data extraction forms a priori as recommended in the *Cochrane Handbook for Systematic Reviews* to extract information on relevant features and results of included studies

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(Higgins 2021). Two review author will independently extract and record the data on the forms. Extracted data will include:

a) Characteristics of children: age, sex, duration of symptoms; specific definition of intractable constipation (explicit definition if stated; if not stated, characteristics of children that led to inclusion as 'intractable' constipation. This may include length of unsuccessful therapy prior to enrolment, the number of therapies tried without success, or a combination, as described by the primary study).

b) Study methods, total number of participants originally assigned to each treatment group

c) Intervention: preparations, doses, administration regimen, description of the intervention (if non-medical)

d) Control: placebo, other drugs, other interventions

e) Concurrent medications or other interventions

f) Outcomes: time of assessment, length of follow-up, frequency of defecation, pain or straining on defecation, faecal incontinence, stool consistency, need for additional therapies or interventions, number and type of adverse events associated with the treatment or intervention

h) Withdrawals and reasons for withdrawals

Assessment of risk of bias in included studies

Two review authors will independently assess the methodological quality of included trials using the Cochrane risk of bias tool (Higgins 2021). Factors assessed will include:

- Sequence generation (i.e. was the allocation sequence generation adequately randomised?)
- Allocation sequence concealment (i.e. was allocation adequately concealed?)
- Blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?)
- Incomplete outcome data (i.e. were incomplete outcome data adequately addressed?)
- Selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?)
- Other potential sources of bias (i.e. was the study apparently free of other problems that could put it at high risk of bias?)

A judgement of yes indicates a low risk of bias, no indicates a high risk of bias, and unclear indicates an unclear or unknown risk of bias. We will resolve disagreements by consensus. We will contact study authors for further information when insufficient information is provided in the report to determine the risk of bias.

Measures of treatment effect

For dichotomous outcomes, we will assess all dichotomous outcomes by calculating the risk ratio (RR) and 95% CI, using a random-effects model.

For continuous outcomes, we will assess all secondary outcomes calculating the mean difference (MD) and 95% confidence interval (CI), when using the same units. When different scales are used to evaluate the same outcome, we will calculate the standardised mean difference (SMD) and 95% CI. We will pool studies using a random-effects model.

Unit of analysis issues

The participant will be the unit of analysis. For studies comparing more than two intervention groups, we will make multiple pair-wise comparisons between all possible pairs of intervention groups. To avoid double-counting, we will divide shared intervention groups evenly among the comparisons. For dichotomous outcomes, we will divide both the number of events and the total number of participants. For continuous outcomes, we will only divide the total number of participants, and leave the means and standard deviations unchanged.

We will only include cross-over studies if data are separately reported before and after cross over, and will use only pre-cross-over data. We do not anticipate finding any cluster-RCTs; however, we will only use study data if the authors have used appropriate statistical methods in taking clustering effect into account. We will also exclude cluster-RCTs in a sensitivity analysis to assess their impact on the results.

Dealing with missing data

We will contact the authors of included studies to request any missing data. We will attempt to estimate missing standard deviations using relevant statistical tools and calculators available in Review Manager 5 if studies report standard errors (Review Manager 2020). We will judge studies that fail to report measures of variance at high risk of selective reporting bias.

Assessment of heterogeneity

We will assess heterogeneity among trials by visual inspection of forest plots, and by calculating the Chi^2 test for heterogeneity (we will consider a P value of 0.05 as statistically significant). We will also use the I^2 statistic to quantify the effect of heterogeneity (Higgins 2003). We will use a random-effects model, and further analyse using a fixed-effect model to further investigate heterogeneity. We will interpret the thresholds as follows (Higgins 2021):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication bias. We will use Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We will consider a P value < 0.05 to be a statistically significant reporting bias.

Data synthesis

We will combine data from individual trials in a meta-analysis if the interventions, participant groups, and outcomes are sufficiently similar (determined by consensus). We will calculate the pooled RR and corresponding 95% CI for dichotomous outcomes. We will conduct the meta-analyses using a random-effects model. We will not pool data in a meta-analysis if we detect a considerable degree of heterogeneity (i.e. $I^2 > 75\%$).

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Given the diversity of interventions available for the treatment of constipation, we will group interventions for analysis using the following classifications:

- Laxative therapy (where single agents are administered)
- Laxative therapy (where combination therapy is administered)
- Colonic irrigation
- Surgical interventions (e.g. antegrade colonic enema)
- Non-laxative pharmacological therapy (e.g. botulinum toxin injection, other pharmacological agents)
- Alternative therapies

We will use Cochrane Review Manager 5 software for data analysis (Review Manager 2020). We will analyse data according to the intention-to-treat principle. We will assume that participants with final missing outcomes are treatment failures.

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses to further study the effects of a number of variables on the outcomes including:

- By specific medication preparation
- The effect of length of therapy and follow-up
- The specific characteristics of participants' intractable constipation; subgroup may be by length of unsuccessful therapy prior to enrolment, or by number or types of failed therapies prior to enrolment
- By definition used to define intractable constipation

Sensitivity analysis

Where possible, we will undertake sensitivity analyses on the primary outcomes to assess whether the findings of the review are robust to the decisions made during the review process.

In particular, we will exclude studies at high or unclear risk of selection bias due to allocation bias and performance bias from analyses with studies with different risk of bias judgments.

Where data analyses include studies with reported and estimated standard deviations, we will exclude those with estimated standard deviations, to assess whether this affects the findings of the review. We will investigate whether the choice of model (fixed versus random) may affect results, as well as studies published in full versus abstract.

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables for all primary outcomes.

We will use the five GRADE considerations (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias), to assess the certainty of the evidence, based on the studies that contributed data to the meta-analyses for each outcome, classifying the certainty as high (i.e. further research is very unlikely to change our confidence in the estimate of effect), moderate (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (i.e. we are very uncertain about the estimate) (Higgins 2021). We will use the GRADEpro GDT software (GRADEpro GDT). We will justify all decisions to downgrade the certainty of the evidence in footnotes, and provide comments to aid the reader's understanding of the review where necessary.

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Dr. Yuhong Yuan (Information Specialist at the Cochrane Gut Group) designed the search strategies for CENTRAL, MEDLINE, and Embase.

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APPENDICES

Appendix 1. CENTRAL Ovid search strategy

1. exp Constipation/
2. constipation.tw,kw.
3. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kw.
4. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kw.
5. (obstipation or colon transit or defecation or defaecation).tw,kw.
6. or/1-5
7. (intractable or unmanageable or uncontrollable or difficult to control or chronic).tw,kw.
8. (((non or "not") adj3 (responsive* or respond*)) or unrespond* or unrespons* or nonrespond* or nonrespons*).tw,kw.
9. exp Recurrence/
10. (recurren* or recurred or relaps* or recrudescence* or refractor* or reoccur* or redelop* or exacerbate* or reappear* or return* or progress* or periodic or persist* or deteriorate*).tw,kw.
11. (refractory or refractories).tw,kw.
12. (failure or failed or ((after or following) adj2 (fail* or first line or withdraw* or withdr* or cessation or stop* or discontin* or de-escalation))).tw,kw.
13. exp Salvage Therapy/
14. exp Retreatment/
15. (retreat* or re-treat* or salvage or rescue or reintroduction*).tw,kw.
16. or/7-15
17. 6 and 16
18. exp Adolescent/
19. exp Child/
20. exp Infant/
21. exp Minors/
22. exp Pediatrics/
23. exp Puberty/

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24. exp Schools/
25. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
26. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
27. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
28. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
29. or/18-28
30. 17 and 29

Appendix 2. MEDLINE Ovid search strategy

1. exp Constipation/
2. constipation.tw,kw.
3. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kw.
4. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kw.
5. (obstipation or colon transit or defecation or defaecation).tw,kw.
6. or/1-5
7. (intractable or unmanageable or uncontrollable or difficult to control or chronic).tw,kw.
8. (((non or "not") adj3 (responsive* or respond*)) or unrespond* or unrespons* or nonrespond* or nonrespons*).tw,kw.
9. exp Recurrence/
10. (recurren* or recurred or relaps* or recrudescence* or refractor* or reoccur* or redelop* or exacerbate* or reappear* or return* or progress* or periodic or persist* or deteriorate*).tw,kw.
11. (refractory or refractories).tw,kw.
12. (failure or failed or ((after or following) adj2 (fail* or first line or withdraw* or withdr* or cessation or stop* or discontin* or de-escalation))).tw,kw.
13. exp Salvage Therapy/
14. exp Retreatment/
15. (retreat* or re-treat* or salvage or rescue or reintroduction*).tw,kw.
16. or/7-15
17. 6 and 16
18. exp Adolescent/
19. exp Child/
20. exp Infant/
21. exp Minors/
22. exp Pediatrics/
23. exp Puberty/
24. exp Schools/
25. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
26. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
27. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
28. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
29. or/18-28
30. 17 and 29
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.
37. trial.ab.

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38.groups.ab.
39.or/31-38
40.exp animals/ not humans.sh.
41.39 not 40
42.30 and 41

Note: Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

Appendix 3. Embase Ovid search strategy

1. exp constipation/
2. constipation.tw,kw.
3. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kw.
4. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kw.
5. (obstipation or colon transit or defecation or defaecation).tw,kw.
6. or/1-5
7. (intractable or unmanageable or uncontrollable or difficult to control or chronic).tw,kw.
8. (((non or "not") adj3 (responsive* or respond*)) or unrespond* or unrespons* or nonrespond* or nonrespons*).tw,kw.
9. exp recurrent disease/
10. (recurren* or recurred or relaps* or recrudescence* or refractor* or reoccur* or redelop* or exacerbate* or reappear* or return* or progress* or periodic or persist* or deteriorate*).tw,kw.
11. (refractory or refractories).tw,kw.
12. (failure or failed or ((after or following) adj2 (fail* or first line or withdraw* or withdr* or cessation or stop* or discontin* or de-escalation))).tw,kw.
13. exp salvage therapy/
14. exp retreatment/
15. (retreat* or re-treat* or salvage or rescue or reintroduction*).tw,kw.
16. or/7-15
17. 6 and 16
18. exp adolescence/ or exp adolescent/
19. exp child/
20. exp newborn/
21. exp kindergarten/
22. exp pediatrics/
23. exp puberty/
24. exp school/
25. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
26. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
27. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
28. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
29. or/18-28
30. 17 and 29
31. random:.tw.
32. placebo:.mp.
33. double-blind:.mp.
34. or/31-33
35. exp animal/ not human.sh.
36. 34 not 35
37. 30 and 36

Note: Two or more terms min difference RCT filter for EMBASE: hiru.mcmaster.ca/hiru/hedges/All-EMBASE.htm

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CONTRIBUTIONS OF AUTHORS

MG conceived the review and contributed to the planning and writing

CGC contributed to the writing and approved the manuscript

SR led the write-up of the protocol and approved the manuscript

MB contributed content and speciality expertise to the protocol and approved the manuscript

VS contributed to the methods and protocol design and approved the manuscript

AA contributed to the writing and approved the manuscript

DECLARATIONS OF INTEREST

MG: Since August 2016, I received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role, or any other relationship, and were restricted to the travel and meeting-related costs of attending such meetings. The companies include: Biogaia (2017 to 2019), Ferring (2018), Allergan (2017), Synergy (bankrupt in 2018), and Tillots (2017 to 2019). None of these companies had any involvement in any works completed by me, and I have never had any payment for any other activities for them, as confirmed below. From these date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form, for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters, and is reported in line with these policies.

CGC has none to declare

SR has none to declare.

MAB is a consultant for Shire, Sucampo, Takeda, AstraZeneca, Norgine, Coloplast, Allergan, Danone, Novalac, Sensus, and FrieslandCampina.

VS has none to declare

AA has none to declare

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