BMJ Paediatrics Open

ESPGHAN and NASPGHAN 2023 protocol for paediatric FAPD treatment guidelines (standard operating procedure)

Morris Gordon ,[1] Marc A Benninga,[2] Rachel Borlack,[3] Osvaldo Borrelli,[4] Ashish Chogle,[5] Anil Darbari,[6] Jernej Dolinsek,[7] Jip Groen,[8] Julie Khlevner,[9] Carlo Di Lorenzo,[10] Hannibal Person,[11] Miguel Saps,[12] Vassiliki Sinopoulou ,[1] Julie Snyder,[13] Merit Tabbers,[14] Nikhil Thapar,[15] Arine Vlieger[16]

To cite: Gordon M, Benninga MA, Borlack R, *et al*. ESPGHAN and NASPGHAN 2023 protocol for paediatric FAPD treatment guidelines (standard operating procedure). *BMJ Paediatrics Open* 2023;**7**:e002166. doi:10.1136/bmjpo-2023-002166

Received 1 July 2023
Accepted 28 November 2023

For numbered affiliations see end of article.

Correspondence to
Professor Morris Gordon; Mgordon@uclan.ac.uk

ABSTRACT

Introduction To date, no international guidelines have been published for the treatment of paediatric functional abdominal pain disorders (FAPDs), subcategorised into functional abdominal pain–not otherwise specified (FAP-NOS), irritable bowel syndrome (IBS), functional dyspepsia and abdominal migraine (AM). We aim for a treatment guideline, focusing on FAP-NOS, IBS and AM, that appreciates the extensive array of available therapies in this field. We present the prospective operating procedure and technical summary protocol in this manuscript.

Methods Grading of Recommendations, Assessment, Development and Evaluation (GRADE) will be followed in the development of the guideline, following the approach as laid out in the GRADE handbook, supported by the WHO. The Guideline Development Group (GDG) is formed by paediatric gastroenterologists from both the European Society for Pediatric Gastroenterology, Hepatology and Nutrition, as well as the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Also, one clinical psychologist with expertise in FAPDs is a voting member in the GDG. A final consensus list of treatment options is translated into 'patient, intervention, comparison, outcome' format options. Prospective agreement on the magnitude of health benefits or harms categories was reached through a Delphi process among the GDG to support grading of the literature.

There will be a detailed technical evidence review with randomised controlled trial data that will be judged for risk of bias with the Cochrane tool. Recommendations are preferably based on GRADE but could also be best practice statements following the available evidence. A full Delphi process will be used to make recommendations using online response systems. This set of procedures has been approved by all members of the GDG.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Abundant therapeutic approaches exist for functional abdominal pain disorders in children.

⇒ However, a lack of international consensus on best evidence-based practice prevents optimal treatment of these disorders.

WHAT THIS STUDY ADDS

⇒ The prospective publishing of this document is part of the process of systematic guideline production.

⇒ This manuscript describes the prospectively agreed methods and operating procedures that will be followed to produce the new treatment guideline for functional abdominal pain–not otherwise specified (FAP-NOS), irritable bowel syndrome (IBS) and abdominal migraine (AM).

⇒ It also describes how the Guideline Development Group (GDG) was created and the process related to organisation, planning and training of the GDG. This technical summary protocol describes the process of generating the 'patient, intervention, comparison, outcome' thematic questions. This set of procedures has been approved by all members of the GDG. Several methodological elements are novel within the field.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We aim for this guideline to provide a tool for the treatment of children aged 4–18 years with FAP-NOS, IBS and AM worldwide for all treatment settings.

⇒ This could lead to more uniformity in treatment, as well as yield more capacity for collaboration in a scientific setting worldwide.

INTRODUCTION

Functional abdominal pain disorders (FAPDs) are common in children, with a worldwide pooled prevalence of 13.5% for ages 4–18 years and a small, but consistent predisposition in girls over boys (15.9% vs 11.5%).[1] FAPDs are categorised into four subtypes, that is, functional abdominal pain–not otherwise specified (FAP-NOS), irritable bowel syndrome (IBS), functional dyspepsia (FD) and abdominal migraine (AM).[2] Although each subtype is recognised as a separate entity, there is some degree of

overlap among them. This overlap particularly applies for FAP-NOS and IBS, both in clinical presentation, as well as in treatment options and response. Children diagnosed with FAP-NOS exhibit similar characteristics to those with paediatric IBS in terms of pain frequency and intensity, quality of life, and symptoms of anxiety and depression. Therefore, distinguishing between these two entities based on these factors alone is not possible.[3] Management of FAP-NOS and IBS in children is focused on multidisciplinary approaches, including dietary modifications, gut–brain psychotherapies, pharmacological treatments, probiotics and percutaneous electrical nerve field stimulation.[4] Functional dyspepsia is subdivided into postprandial distress syndrome and epigastric pain syndrome, with the mainstay for treatment being prokinetic medication, proton pump inhibitors and neuromodulators, thus representing an evidently distinct category of disease, while still regarded an abdominal pain condition following Rome IV criteria.[5] AM presents with paroxysmal abdominal pain episodes, lasting for at least 1 hour and for which treatment is mostly based on analgesic medication to alleviate symptoms in the short period they occur.[5] Symptomatic episodes may be separated by weeks to even months.[4]

All FAPDs can have severe implications on quality of life, reflected by higher incidences of anxiety and depression and increased consumption of healthcare.[6–9] The burden of FAPDs is reflected by the fact that quality of life is rated similarly low as in inflammatory bowel disease.[10 11] The current understanding of the aetiopathogenesis describes a biopsychosocial model, in which disease arises from a genetic predisposition where both gastrointestinal factors (eg, intestinal dysbiosis, gut inflammation and motility disorders) as well as psychosocial sensitising events (eg, trauma, depression, passive coping mechanisms) lead to structural and functional disruption of the gut–brain axis.[4] These disruptions translate to the core mechanisms for disease, that is, visceral hypersensitivity and central hypervigilance.[4] A delay may exist between disruption of the gut–brain axis and the translation to these core mechanisms and thereby the onset of symptoms, hampering direct causal correlation and better preventive strategies. It is known that a large proportion of children with an FAPD continues to have symptoms into adolescence and adulthood,[12] emphasising the need for targeted treatment approaches and education at the earliest stage possible, as well as preventive strategies.

Members of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) are proposing a joint guideline outlining the therapeutic approach for FAPDs, focusing on FAP-NOS, IBS and AM in children.[2] The decision to exclude FD from the scope of this guideline was made based on its distinct classification as a separate disease category and its notably different treatment approaches. It is deemed necessary to develop a separate treatment guideline specifically dedicated to addressing FD. On the other hand, despite the clear distinctions in overall symptoms between AM and FAP-NOS/IBS, it is impractical to exclude AM as a separate entity from this guideline due to its frequent inclusion in studies involving mixed populations of patients with FAP-NOS and IBS. Therefore, acknowledging its distinguishable characteristics, AM will be considered within the context of this guideline. The nomenclature, diagnostic criteria and therapeutic options have advanced significantly since the last published NASPGHAN position paper on the subject in 2008,[13] with publication of the latest Rome IV criteria for paediatric FAPDs as its foundation.[2] Simultaneously, significant advances have been made in the understanding of pathophysiology of FAPDs including gastrointestinal mechanisms, central and extrinsic factors and the role of the microbiota on the gut–brain axis.[4] Advancements in diagnostic criteria have supported increased homogeneity in clinical trials on this subject, enabling a better systematic review of the available literature, which resulted in proposing an international treatment guideline. The final area of significant development relates to the methodological advances within guideline development, most notably within the procedures of the 'Grading of Recommendations, Assessment, Development and Evaluation' (GRADE) approach to both appraising evidence and producing guidelines.

This protocol describes the prospectively agreed methods and operating procedures that will be followed to produce a GRADE international treatment guideline, covering the multidisciplinary approaches used in clinical practice today. The final guideline will contain the official recommendations of the Guideline Development Group (GDG) on all treatment aspects of FAP-NOS, IBS and AM. It is worth noting that while the search, selection, extraction and analysis may contain studies with limited numbers of patients suffering with FD and therefore this condition is within the scope of the guideline, the guideline will not include recommendations for FD for two reasons. First, recent technical and scoping reviews suggest very few trials exist focusing on the condition, limiting the potential for GRADE recommendations. Second, the presentation of the condition is distinct enough that in trials that include patients with multiple subtypes, they rarely include FD which in turn means any recommendations would not be able to include FD in scope.

The guideline will support patients and professionals in all parts of the world and across different treatment settings and therefore is presented in a fully systematic and transparent fashion. The prospective publishing of this document is part of that process of systematic guideline production.

METHODS

The production of this guideline will follow the procedures of the GRADE approach as laid out in the GRADE

handbook, supported by the WHO handbook for guideline development.[14] The team will use the GIN-McMaster guideline development checklist (McMaster 2021), an 18-point process map to support the steps in a GRADE-compliant guideline development process.[15]

Organisation, planning and training

In July 2022, members of the NASPGHAN GDG discussed a potential collaboration on an FAPD treatment guideline with both members of ESPGHAN and methodological support from the 'Biomedical Evidence Synthesis and Translations to practice' (BEST) Unit at the University of Central Lancashire (which houses the editorial centre for the Cochrane Gut group). Prior to this discussion, NASPGHAN council initially approved the formulation of these guidelines with a set of member authors from NASPGHAN. Evidence synthesis guidance was sought through Cochrane Gut (MG, VS). Delegates of NASPGHAN (AC, MS, AD, JK, CDL) conceived the idea for this international treatment guideline. The protocol was reviewed and edited by the NASPGHAN team. An invitation was extended to ESPGHAN to join the GDG led by MAB and MT. The framework for guideline development was created, outlining that an ESPGHAN core team (MAB, JG, MT) in collaboration with BEST (MG, VS) will be responsible for the technical review, including searches, the tables and synthesis of the result section. Subsequently, a meeting with members of both societies (NASPGHAN and ESPGHAN ref) will be organised, preferably in person but otherwise digital or hybrid, to discuss the results in depth and start the process of formulating recommendations.

The joint guideline chairs will be appointed as content and field experts from both societies (ESPGHAN and NASPGHAN ref) and will be joined with a lead and non-voting GRADE methodologist as co-chair (MG) in line with GRADE procedures.[16] Administrative support will be offered from both host Higher Education Institutions of the co-chairs and access to a Cochrane and National Institute for Health and Care Excellence expert information specialist arranged through these institutions.

Guideline Development Group

The GDG is formed by members of NASPGHAN and ESPGHAN. Included are paediatricians and paediatric gastroenterologists with expertise in FAPD and its treatment. Also, one clinical psychologist with extensive experience in the treatment of children with FAPD is a voting member of the GDG. The methodological chair remains non-voting.

The lead and senior authors for the guidelines were approved by the member societies. All members of the two teams agreed to be coauthors of the full guideline, to maintain the confidentiality of open discussion and debate within the guideline process, as well as the confidentiality of the content of the guideline prior to publication. Members were asked to declare all conflicts of interest relevant to the FAPD guidelines.

GDG priority setting and identifying target audience

A key consideration will be priority for stakeholders for specific clinical or patient factors. Key patient and family stakeholders were consulted through a Delphi process in previous studies to contribute to the formation of a core outcome set for assessing treatment success in FAPDs. This core outcome set forms the basis for this treatment guideline.[17]

Analysis by chairs has led to the final scope of conditions, treatments and outcomes. A final consensus list of thematic questions within a patient, intervention, comparison, outcome (PICO) format was produced and agreed in the final phase of the Delphi process.

Stages of production

The following basic procedures will guide the main stages of the guideline:

- The prospective publishing of a guideline operating procedure and technical summary protocol in an open-access journal (this manuscript).
- Prospective agreement of magnitude of health benefits or harms categories,[18] core outcomes for inclusion and preferably measures for each outcome.
- The completion of a detailed, methodologically rigorous technical review which will include GRADE summary of findings for all outcomes and preparation of evidence to decision (ETD) frameworks to support the GDG decision-making.[19]
- A face-to-face summit of the GDG to discuss the evidence within the ETD. This will be followed by voting anonymously and then further discussion on items with disagreement to reach a consensus.
- The publishing of a succinct main guideline that summarises key recommendations, the certainty of underpinning evidence and the strength of the recommendations all within the main published journal output.
- An accompanying larger detailed technical evidence review that includes all the underpinning primary evidence, secondary synthesis quality and analysis data, also published within the main journal output.

This suite of outputs will offer systematic, high-quality and high-utility output for all our audiences.

PICO question generation

The generation of questions was guided by the JCE GRADE guidelines.[20]

The process of prioritisation has been based on the thematic and PICO questions that have been formulated in systematic reviews on treatment of FAPD, in which the Cochrane team (MG, VS) was involved.[21–24] The generation of new questions was a key component of the Delphi prioritisation, asking for any new or uncovered areas to be presented in free text by the GDG members, with justification of the specific question. Analysis of these results allowed new candidate questions to be considered by the GDG. If new questions were needed, they were produced in a standard PICO format.

Key areas of focus for refinement of all PICO questions have been considered by the GDG. These core elements of refinement around PICO questions and their specific application have been presented in draft form to the GDG and all feedback considered, with the final list below:

- Multiple treatment arms will be considered. To allow consideration of non-placebo comparators and standard therapies, network meta-analysis will be deployed in key targeted areas, as decided by the GDG and when sufficient volume of homogeneous studies is likely to be included. Subgroup analyses will be performed for outcome measures in the case of different comparator groups, given that heterogeneity and sufficient volume of studies exist.
- Outcome measures were based on previous publication of a core outcome set for defining treatment effect in FAPD in children.[17] Following the GRADE handbook, outcomes were defined as critical, important or not important through a Delphi process and a face-to-face meeting held to agree the final set of outcomes in May 2023 (stated below).
- The GDG will outline decision thresholds for FAPD treatment outcome measures before proceeding to data analysis. This will be achieved through a Delphi procedure to identify ranges for trivial, small, moderate and large treatment effect.[19] These ranges will be identified for each of the included outcome measures separately. The upper limit of trivial or lower limit of small treatment effect will serve as primary decision threshold, for consideration of a positive recommendation.
- Therapy delivered in primary, secondary or tertiary care, as well as self-administered, will be considered but setting will be described in the technical summary to allow any clarifying statements to be made regarding the context of evidence.
- Patient, parent or healthcare provider-reported outcomes will be analysed combined. However, if severe heterogeneity and sufficient literature exist, subgroup analysis will be performed.

Evidence selection

Types of studies

All published, unpublished and ongoing randomised controlled trials (RCTs) that compared interventions for the management of FAPD with other active interventions or standard therapy, placebo or no therapy will be considered for inclusion. We will exclude studies that do not report on any of the outcome measures specified below.

Types of participants

Trials enrolling children from the age of 4 to 18 years, with a clinical FAP-NOS, IBS or AM diagnosis as defined by the Rome criteria (table 1), will be considered for inclusion.[2] If studies do not define subgroups within FAPD, authors will be contacted for discriminatory data, but studies will still be included if they do not provide this. If studies include a mix of adults and children and the data are not separated, authors will be contacted, and the study only included if separate data on children can be provided upon request.

Types of interventions

Trials studying the interventions outlined in tables 2 and 3 can be included.

Types of outcome measures

Both dichotomous and continuous outcomes will be valid for inclusion. Ranking of the outcome measures was based on the core outcome set,[17] with the core research team (MG, VS, JG, MT, MAB) proposing a final ranking that received the consent of all GDG members. The set of outcomes includes a mix of outcomes pertaining to the efficacy of treatment (ie, the success of a treatment in reducing symptoms and any consequent beneficial sequelae) and to the safety of a treatment (ie, any outcome related to adverse events or their sequelae).

Primary (critical) outcomes (assessed before and after start of treatment)

- Treatment success as defined by the authors.
- Abdominal pain frequency or change in frequency of pain using any validated scale.
- Abdominal pain intensity or change in pain intensity using any validated scale.
- Serious adverse events.

Secondary (important) outcomes (assessed before and after start of treatment)

- Quality of life or change in quality of life measured using any validated measurement tool.
- Change in stool consistency (Bristol Stool Scale).
- Total adverse events withdrawal due to adverse events.
- Neither important nor critical outcomes (therefore not included in the technical review).
- Anxiety/depression.
- Adequate relief.
- School attendance or change in school attendance or performance.

Thresholds for outcomes

For each of the included outcomes, a Delphi process was ran among the GDG. Each member was asked to identify the following for each outcome when considering a comparison of an intervention and a placebo/no intervention/other interventions:

- The minimum threshold for a small difference to be defined (lower than this would be 'trivial').
- The minimum threshold for a moderate difference to be defined (lower than this would be 'small').
- The minimum threshold for a large difference to be defined (lower than this would be 'moderate' and all above this would be 'large').

The GDG was asked to conceptualise this from the perspective of their existing working knowledge of clinical difference, how these would be presented and

Table 1 Diagnostic criteria for FAP-NOS, IBS and AM according to the Rome IV criteria[5]

Diagnosis	Criteria
FAP-NOS	Must include all of the following criteria, being fulfilled at least 4 times per month and for at least 2 months prior to diagnosis:
	1. Episodic or continuous abdominal pain that does not occur solely during physiological events (eg, eating, menses)
	2. Insufficient criteria for IBS, functional dyspepsia or AM
	3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition
IBS	Must include all of the following criteria, being fulfilled for at least 2 months prior to diagnosis:
	1. Abdominal pain at least 4 days per month over at least 2 months associated with *one or more* of the following:
	a. Related to defecation
	b. A change in frequency of stool
	c. A change in form (appearance) of stool
	2. In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)
	3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
AM	Must include all of the following occurring at least twice: *Criteria fulfilled for at least 6 months prior to diagnosis*
	1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
	2. Episodes are separated by weeks to months
	3. The pain is incapacitating and interferes with normal activities
	4. Stereotypical pattern and symptoms in the individual patient
	5. The pain is associated with two or more of the following: a. Anorexia b. Nausea c. Vomiting d. Headache e. Photophobia f. Pallor
	6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

AM, abdominal migraine; FAP-NOS, functional abdominal pain–not otherwise specified; IBS, irritable bowel syndrome.

explained to patients and how they would interpret research findings.

The results were presented and discussed at a face-to-face GDG meeting in May 2023. There was very good alignment in almost all outcomes and the means were very similar for all efficacy outcomes, defining a minimum 'small' difference at 11% or greater, a minimum 'moderate' difference at 25% or greater and finally a minimum 'large' difference at 40% or greater.

For safety outcomes, there was less good alignment for minor or total adverse events at 5% for small, 9% for moderate and 17% for large. However, there was poor alignment for serious or withdrawal due to serious events. These had a range from 0.1% up to 15%. A discussion was held and a consensus agreed at thresholds of 1% for a small difference, 3% for moderate and 5% for large.

Search methods for identification of studies

Electronic searches

We will use a search strategy designed and checked by an information specialist with Cochrane expertise.

We will search: the Cochrane Central Register of Controlled Trials (via Ovid EBMR) (inception–present); MEDLINE (via Ovid) (1946–present); PsycINFO (via Ovid) (1987–present); AMED (via Ovid) (Allied and Complementary Medicine) (1985–present); Cumulative Index to Nursing and Allied Health Literature (via EBSCO) (1984–present).

Table 2 Types of pharmacological interventions for FAPDs

Type	Group
Antispasmodics	Peppermint oil
	Drotaverine
	Mebeverine
	Trimebutine
	Hyoscine butylbromide
	Dicyclomine
	Hyoscyamine
Neuromodulators	Amitriptyline
	Citalopram
	Mirtazapine
	Gabapentin
	Pregabalin
Laxatives	Osmotic (polyethylene glycol, lactulose, lactitol)
	Stimulant (bisacodyl, senna, sodium picosulfate)
	Lubricants (mineral oil, paraffin)
	Secretagogues and prokinetic laxatives (linaclotide, lubiprostone, prucalopride, plecanatide)
	Tegaserod, alosetron
Enemas	
Anti-diarrhoeal medication	Loperamide
Antibiotics	
Analgesics	Paracetamol/acetaminophen, non-steroidal anti-inflammatory drugs, tramadol
Anti-reflux medication	PPI, H2-receptor antagonist, prokinetics, domperidone)
Anti-emetics	
Antimigraine medication	Sumatriptan, propranolol
Antihistamines	Cyproheptadine, ebastine
Serotonin agonist	Buspirone
Melatonin	
Opioid agonist	Eluxadoline
Serum bovine-derived immunoglobulin	
Bile acid sequestrants	

FAPDs, functional abdominal pain disorders; PPI, proton pump inhibitor.

Table 3 Types of non-pharmacological interventions for FAPDs

Type	Group
Lifestyle advice including physical activity	
Dietary interventions	Extra fluid intake
	Fibre
	Low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols FODMAP diet
	Fructans
	Fructose-restricted diet
	Prebiotics (inulin)
	Lactose-free diet
	Dairy-free diet
	Gluten-free diet
	Histamine low or free diet
	Multiple exclusion diet
	Decrease in gas-producing foods
	Vitamin D
Probiotics and synbiotics	Identified to species level
Herbs, iberogast	
Behavioural therapies	Hypnotherapy/guided imagery
	Cognitive–behavioural therapy (incl. exposure therapy)
	Mindfulness
Complementary therapy	Acupuncture
	Homeopathy
	Body-oriented therapy
	Musculoskeletal therapy (osteopathy/chiropractic)
	Yoga
	Auriculotherapy
	Acupressure
	Acutherapy
Biofeedback	
Neurostimulation	

FAPDs, functional abdominal pain disorders.

We will place no restrictions on language of publication.

Given the lead methodological team's familiarity with the literature and its scope from recent guideline production at national level, it was decided that the inclusion of systematic reviews is not required. Instead, primary studies will be included and all syntheses and appraisal completed.

RCTs that assess the interventions of interest will be included for consideration. Only studies that use conventional dose regimens in at least one treatment arm will be considered for inclusion. Phase 1 studies will not be included. Studies must be randomised—with quasi-randomised or non-randomised studies not included. These studies will be extracted and analysed as per the methods below and where appropriate, combined with the systematic reviews above.

As complementary search methods, we will carefully check relevant systematic reviews for potentially eligible studies. We will also scrutinise the references of included studies. We will search unpublished trials by contacting experts in the field, and scan the internet and abstracts submitted to major international congresses from the 2 years prior to the search to capture any studies presented but not yet published in full. In the case of

foreign language papers, we plan to obtain translations of papers if necessary.

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.[25]

Selection of studies

A PhD student (JG) working in the Emma Children's Hospital, Amsterdam University Medical Centres, Amsterdam, the Netherlands, in collaboration with the Cochrane team (MG, VS) and supporting fellows or healthcare students, will independently screen the titles and abstracts identified by the literature search, excluding studies that based on title and abstract did not meet our inclusion criteria. All will be screened in duplicate independently and disagreements solved by a third author. They will obtain the full reports of studies deemed potentially eligible. These reviewers will independently assess the full texts for inclusion in the review. Any disagreements will again be resolved by discussion or by consulting another review author (MT/MAB) if necessary. We will record the studies excluded at this or subsequent stages, and the main reason for their exclusion, in the 'Characteristics of excluded studies' tables.

Where there are multiple publications for a given study, we will collate the reports of the same study so that each study, rather than each report, will be the unit of interest in the review; such studies have a single identifier with multiple references.

Data extraction and management

The PhD student (JG) and members of the Cochrane team (MG, VS) will independently perform data extraction using piloted data extraction forms. We will extract the following data from the included studies:

- Trial setting: country and number of trial centres.
- Methods: study design, total study duration and date.
- Participant characteristics: age, sociodemographics, FAPD subcategory and total number of participants.
- Eligibility criteria: inclusion and exclusion criteria.
- Intervention and comparator description.
- Outcomes: outcome definition, unit of measurement and time of collection.
- Results: number of participants allocated to each group, missing participants and sample size.
- Funding source.

All treatment arms are described in the 'Characteristics of included studies' tables.

Assessment of risk of bias in included studies

More than two authors will independently assess risk of bias in the included studies based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[25]

We will assess the following 'risk of bias' domains:

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other biases such as imbalance in participants' baseline characteristics.

The studies will be judged to be at low, high or unclear risk of bias for each domain assessed, based on the guidance in the Cochrane Handbook for Systematic Reviews of Interventions.[25]

After data extraction, the review authors will compare the extracted data, discussing and resolving any discrepancies before transfer of data into the 'Characteristics of included studies' tables.

Measures of treatment effect

We will express treatment effect as risk ratios (RRs) with corresponding 95% CIs for dichotomous outcomes, and mean difference (MD) with 95% CI for continuous outcomes. Where endpoint and change scores were both reported, we will use endpoint scores for data analysis. However, if the studies assessed the same continuous outcome in different ways, we will estimate the treatment effect using the standardised MD (SMD).[26]

Unit of analysis issues

The unit of analysis is the participant. For studies comparing more than two intervention groups, we plan to make multiple pairwise comparisons between all possible pairs of intervention groups. To avoid double-counting, we would divide shared intervention groups evenly among the comparisons. For dichotomous outcomes, we plan to 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 SDs unchanged. We plan to include crossover studies for quantitative analysis only if data were separately reported before and after crossover and use only pre-crossover data. We do not anticipate finding any cluster-RCTs; we would only use study data from such trials if the authors employed appropriate statistical methods in taking the clustering effect into account. We would also exclude cluster-RCTs in a sensitivity analysis to assess their impact on the results.

Dealing with missing data

We will contact study authors in the case of missing data or studies that did not report data in sufficient detail. We will attempt to estimate missing SDs using relevant statistical tools and calculators available in Review Manager V.5 if studies reported SEs (Review Manager 2020). Studies that failed to report measures of variance will be judged as at high risk of reporting bias.

Assessment of heterogeneity

We will assess the included studies to determine their homogeneity in terms of participants, intervention, comparator and outcome. To test for statistical

heterogeneity, we will employ a X^2 test using a p value of less than 0.1 to give an indication of the presence of heterogeneity. Inconsistency was quantified and represented by the I^2 statistic. We will interpret the thresholds as follows[25]:

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

Assessment of reporting biases

Most reporting biases are minimised by using an inclusive search strategy. We plan to investigate publication bias using a funnel plot if there were 10 or more studies. The magnitude of publication bias would be determined by visual inspection of the asymmetry of the funnel plot. In addition, we would test funnel plot asymmetry by performing a linear regression of intervention effect estimate against its SE, weighted by the inverse of the variance of the intervention effect estimate.[27]

Data synthesis

To summarise the study characteristics, we will conduct a narrative synthesis of all the included studies. We then will carry out a meta-analysis if two or more studies assessed similar populations, interventions and outcomes. We plan to analyse studies of children and different subintervention types separately. We will use Review Manager V.5. We will synthesise study data using the random-effects model. We will combine effect estimates of studies that reported data in a similar way in the meta-analysis. We will pool RRs for dichotomous outcomes, and MDs or SMDs for continuous outcomes, alongside 95% CIs. Where we are unable to carry out a meta-analysis (eg, due to lack of uniformity in data reporting), we will present a narrative summary of the included studies.

Subgroup analysis and investigation of heterogeneity

If we identify heterogeneity, we will investigate possible causes and address them using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[25] We plan to undertake subgroup analyses of potential effect modifiers if sufficient data were available. We have identified several potential modifiers of effect:

- Subtype of FAPD.
- Age of child (4–11 or 12–18 years).
- Length of disease.
- Length of follow-up.
- Outcome-reporting party (ie, patient, parent, healthcare provider).
- Variation within preclassified treatment options (eg, probiotic strain, differences in applied behavioural therapy).
- Various comparator groups in studied psychosocial interventions (eg, placebo, waiting list patients, regular physical consultation).

Sensitivity analysis

We plan to undertake a sensitivity analysis on the primary outcome of treatment success to assess whether the findings of the review were robust to decisions made during the review process. We plan to exclude studies at high or unclear risk of bias from analyses. Where data analyses included studies with reported and estimated SDs, we will exclude studies with estimated SDs to assess whether this affected the findings of the review. We will investigate whether the choice of model (fixed-effect vs random-effects) affected the results. Finally, in the case of unexplained heterogeneity, targeted consideration of key factors above will be completed on any outlying studies to explore and attempt to define the source of this heterogeneity.

Summary of findings and assessment of the certainty of the evidence

We will present our primary outcome results in 'Summary of findings' tables. Each comparison and primary outcome were exported to GRADEpro GDT software for quality assessment (GRADEpro GDT). Based on risk of bias, inconsistency, imprecision, indirectness and publication bias, we will grade the quality of the evidence for each outcome as high, moderate, low or very low. These ratings have been defined as follows:

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: 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.
- Very low: any estimate of effect is very uncertain.

We will justify all decisions to downgrade the quality of studies using footnotes and make comments to aid the reader's understanding of the review where necessary.

Development of recommendations

The full technical summary will be given to voting members, after an update search is completed to gather any new studies and integrate these into the evidence.

The data and GRADE summary of findings tables will be added to ETD frameworks.[19] These will allow consideration of key factors to inform decision-making. A face-to-face meeting will be held to discuss, explore and critically consider the elements of the technical review completed above and the ETD frameworks.

Where there is clear agreement, recommendations will be prepared, followed by anonymous voting to confirm agreement. Where there is disagreement, the ETD framework will be used to guide voting and identify the underlying reasons for disagreement. The team will then meet and discuss these findings and attempt to prepare any pertinent consensus recommendations. Where agreement cannot be made, this will also be included in the discussion of the guideline.

The non-voting team will refine this into a final list of recommendations and ensure the strength of the recommendations to be made is consistent with the evidence presented and views of the GDG, as per the GRADE recommendation guidance.

The final proposals will be agreed by a consensus, with the strength of agreement, certainty of evidence and strength of recommendations all presented.

The final synthesised recommendations will be prepared in a guideline to meet the ESPGHAN/NASPGHAN and journal publication standards. The ETD frameworks will be made available at supplemental material and the technical evidence published in full as concomitant outputs to support the main guidance.

Author affiliations
[1]University of Central Lancashire, Preston, UK
[2]Emma Children's Hospital UMC, Amsterdam, The Netherlands
[3]Children's Hospital at Montefiore, New York, New York, USA
[4]Great Ormond Street Hospital for Children, London, UK
[5]Children's Hospital of Orange County, Orange, California, USA
[6]Children's National, Washington, District of Columbia, USA
[7]University Medical Centre Maribor, Maribor, Slovenia
[8]VU University Medical Centre Amsterdam, Amsterdam, The Netherlands
[9]Division of Pediatric Gastroenterology, Hepatology and Nutrition, New York Presbyterian Morgan Stanley Children's Hospital, New York, New York, USA
[10]Division of Gastroenterology, Hepatology and Nutrition, Nationwide Children's Hospital, Columbus, Ohio, USA
[11]Seattle Children's Hospital, Seattle, Washington, USA
[12]University of Miami Miller School of Medicine, Miami, Florida, USA
[13]Harvard Medical School, Boston, Massachusetts, USA
[14]Amsterdam University Medical Centres, Duivendrecht, The Netherlands
[15]Queensland Children's Hospital, South Brisbane, Queensland, Australia
[16]Department of Paediatrics, St Antonius Hospital, Nieuwegein, The Netherlands

Twitter Morris Gordon @drmorrisgordon

Contributors Delegates of NASPGHAN (AC, MS, AD, JK, CDL) conceived the idea for this international treatment guideline. Evidence synthesis guidance was sought through Cochrane Gut (MG, VS). MG designed the protocol in initial draft form to support the approval of the guideline process. An invitation was extended to ESPGHAN to join the Guideline Development Group led by MAB and MT. Both paediatric societies have invested in the development of this guideline. An original draft for this protocol manuscript was made by MG with JG, and then finalised by the Cochrane team (MG, VS) and the core research team from ESPGHAN (MAB, MT). For the guideline development, the core research team from ESPGHAN (MAB, JG, MT) will provide overall direction and planning. The Cochrane team (MG, VS) will verify the analytical methods and support the overall execution. Coauthors MAB, RB, OB, AC, AD, JD, JK, CDL, HP, MS, JS, MT, NT and AV agreed on the review questions, approved the protocol and contributed to the final version of this manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. A small fee was made available through the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) for travel expenses to facilitate physical meetings. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) covered travel expenses to facilitate the face-to-face summit for its delegates.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval As a protocol for a guideline not involving primary data or patients, there are no ethical implications and no approval needed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Morris Gordon http://orcid.org/0000-0002-1216-5158
Vassiliki Sinopoulou http://orcid.org/0000-0002-2831-9406

REFERENCES

1 Korterink JJ, Diederen K, Benninga MA, *et al*. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One* 2015;10:e0126982.
2 Hyams JS, Di Lorenzo C, Saps M, *et al*. Functional disorders: children and adolescents. *Gastroenterology* 2016:S0016-5085(16)00181-5.
3 Rutten J, Benninga MA, Vlieger AM. IBS and FAPS in children: A comparison of psychological and clinical characteristics. *J Pediatr Gastroenterol Nutr* 2014;59:493–9.
4 Thapar N, Benninga MA, Crowell MD, *et al*. Paediatric functional abdominal pain disorders. *Nat Rev Dis Primers* 2020;6:89.
5 Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology* 2016;150:1262–1279.
6 Levy RL, Whitehead WE, Walker LS, *et al*. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterol* 2004;99:2442–51.
7 Newton E, Schosheim A, Patel S, *et al*. The role of psychological factors in pediatric functional abdominal pain disorders. *Neurogastroenterol Motil* 2019;31:e13538.
8 Zernikow B, Wager J, Hechler T, *et al*. Characteristics of highly impaired children with severe chronic pain: a 5-year retrospective study on 2249 pediatric pain patients. *BMC Pediatr* 2012;12:54.
9 Lindley KJ, Glaser D, Milla PJ. Consumerism in Healthcare can be detrimental to child health: lessons from children with functional abdominal pain. *Arch Dis Child* 2005;90:335–7.
10 Varni JW, Lane MM, Burwinkle TM, *et al*. Health-related quality of life in pediatric patients with irritable bowel syndrome: a comparative analysis. *J Dev Behav Pediatr* 2006;27:451–8.
11 Youssef NN, Murphy TG, Langseder AL, *et al*. Quality of life for children with functional abdominal pain: a comparison study of patients' and parents' perceptions. *Pediatrics* 2006;117:54–9.
12 Horst S, Shelby G, Anderson J, *et al*. Predicting persistence of functional abdominal pain from childhood into young adulthood. *Clin Gastroenterol Hepatol* 2014;12:2026–32.
13 Nurko S, Di Lorenzo C. Functional abdominal pain: time to get together and move forward. *J Pediatr Gastroenterol Nutr* 2008;47:679–80.
14 World Health O. *WHO handbook for guideline development*.2nd ed. Geneva: World Health Organization, 2014.
15 Schünemann HJ, Wiercioch W, Etxeandia I, *et al*. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ* 2014;186:E123–42.
16 Fretheim A, Schünemann HJ, Oxman AD. Improving the use of research evidence in guideline development: 3. Group composition and consultation process. *Health Res Policy Syst* 2006;4:15.
17 Zeevenhooven J, Rexwinkel R, Van Berge Henegouwen VWA, *et al*. A core outcome set for clinical trials in pediatric functional abdominal pain disorders. *J Pediatr* 2020;221:115–22.
18 Alonso-Coello P, Oxman AD, Moberg J, *et al*. GRADE evidence to decision (Etd) frameworks: a systematic and transparent approach to making well informed Healthcare choices. 2: clinical practice guidelines. *BMJ* 2016;353:i2089.
19 Alonso-Coello P, Oxman AD, Moberg J, *et al*. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016;353:i2016.
20 Guyatt GH, Oxman AD, Schünemann HJ, *et al*. GRADE guidelines: a new series of articles in the Journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.
21 de Bruijn CM, Rexwinkel R, Gordon M, *et al*. Dietary interventions for functional abdominal pain disorders in children: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol* 2022;16:359–71.

22 Gordon M, Sinopoulou V, Tabbers M, *et al*. Psychosocial interventions for the treatment of functional abdominal pain disorders in children: A systematic review and meta-analysis. *JAMA Pediatr* 2022;176:560–8.
23 Gordon M, Farrell M, Thomas AG, *et al*. n.d. Probiotics for management of functional abdominal pain disorders in children. *Cochrane Database Syst Rev*;2023.
24 Rexwinkel R, de Bruijn CMA, Gordon M, *et al*. Pharmacologic treatment in functional abdominal pain disorders in children: A systematic review. *Pediatrics* 2021;147:e2020042101.
25 Cumpston M, Li T, Page MJ, *et al*. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019;10:ED000142.
26 Cohen J. Statistical power analysis for the behavioral sciences. In: *Statistical power analysis for the behavioral sciences*. Academic press, 2013.
27 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.