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REVIEW ARTICLE

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Recommendations for pharmacological clinical trials in children with functional constipation: The Rome foundation pediatric subcommittee on clinical trials

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Abstract

Background: Evidence for the efficacy of commonly used drugs in the treatment of childhood functional constipation (FC) is scarce, studies are often of low quality and study designs are heterogeneous. Thus, recommendations for the design of clinical trials in childhood FC are needed.

Purpose: Members of the Rome Foundation and a member of the Pediatric Committee of the European Medicines Agency formed a committee to create recommendations for the design of clinical trials in children with FC.

Key Recommendations: This committee recommends conducting randomized, double-blind, placebo-controlled, parallel-group clinical trials to assess the efficacy of new drugs for the treatment of childhood FC. Pediatric study participants should be included based on fulfilling the Rome IV criteria for FC. A treatment free run-in period for baseline assessment is recommended. The trial duration should be at least 8 weeks. Treatment success is defined as no longer meeting the Rome IV criteria for FC. Stool consistency should be reported based on the Bristol Stool Scale. Endpoints of drug efficacy need to be tailored to the developmental age of the patient population.

KEYWORDS
children, constipation, pediatrics, RCT, trial

1 | INTRODUCTION

Functional constipation (FC) is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6%.[1] Although the pathophysiology of childhood FC is incompletely understood, an important etiological factor is stool withholding behavior, often occurring after a negative experience associated with stooling—eg, a hard, painful, or frightening bowel movement.[2] Symptoms include infrequent, hard stools, and painful defecation and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence.[3] These symptoms can have a severe impact on a child's quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization.[4-6] Initial non-pharmacological interventions include education, behavioral modifications, and keeping a bowel diary. Despite these interventions, many children require pharmacological interventions.[2] Pharmacological treatment consists of disimpaction (ie, removal of the rectal fecal mass), followed by maintenance treatment and eventually a weaning phase.[2,7] Multiple pharmacological agents are available for the treatment of FC in children.[7,8] Despite chronic pharmacological treatment, approximately 40% of children with FC referred to a pediatric gastroenterologist

remain symptomatic after 5 years and 20% of children still have symptoms after 10 years.[7] In some cases, symptoms may persist into adolescence or adulthood despite medical treatment.[9-11] Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of drugs with action mechanisms that do not address the underlying pathophysiological mechanisms. This relatively poor outcome emphasizes the need for better and more effective treatments of childhood FC.

Currently, the use of several laxatives is based on scarce evidence which is often of low quality.[2,8] Moreover, two recent systematic reviews have shown that the outcomes reported in clinical trials for childhood FC vary greatly among studies.[12,13] This variance in outcome measures and definitions of treatment success makes it difficult to compare study results and to perform meta-analyses. Currently, there are no guidelines or recommendations for pharmacological trials in children with FC. Therefore, the Pediatric Committee on Clinical Trials of the Rome Foundation and a member of the Pediatric Committee of the European Medicines Agency aimed to develop guidelines for the design of clinical trials in children with FC. The objective was to provide recommendations regarding study design, patient selection, concurrent use of medications during trials, documentation, and the use of endpoints. The committee conducted a comprehensive review of the literature and formulated the current recommendations through a consensus process. Two recent systematic reviews on outcome measures used in trials regarding children with FC were used as key literature references.[12,13] After the initial draft of the manuscript was completed by two authors, the manuscript was reviewed and edited by all authors. Based on this initial draft, authors formulated other questions and concerns and consensus on these issues was achieved through phone conferences and face-to-face discussions. This process was repeated several times until all authors agreed with the contents of the current manuscript. The present manuscript does not deal with the design of preclinical, phase I, phase II, or pharmacokinetic studies.

Key Points

- This committee recommends conducting randomized, double-blind, placebo-controlled, parallel-group clinical trials to assess the efficacy of new drugs for the treatment of childhood FC.
- Pediatric study participants should be included based on fulfilling the Rome IV criteria for FC. A treatmentfree run-in period for baseline assessment is recommended. The trial duration should be at least 8 weeks.
- Treatment success is defined as no longer meeting the Rome IV criteria for FC. Stool consistency should be reported based on the Bristol Stool Scale. Endpoints of drug efficacy need to be tailored to the developmental age of the patient population.

2 | RECOMMENDATIONS FOR STUDY DESIGN

Multicenter randomized, double-blind, placebo-controlled, parallel-group, clinical trials are recommended to assess the efficacy of new drugs. The committee recommends double-blind, randomized, placebo-controlled, parallel-group clinical trials to assess the efficacy of therapeutic agents. A parallel design in which each study participant is randomly assigned to a group (intervention or placebo) is recommended. At times, there may be more than two arms, if different doses of the active therapeutic agent are being tested.

Crossover trials are not the design of first choice, as these are at risk of "order effects," where the order in which treatments are given may affect the outcome, and "carry-over" effects, where effects may carry over from one experimental condition to another. A prolonged "wash-out" period between treatments in crossover trials may minimize "carry-over" effects; this strategy would, however, prolong the duration of the trial, potentially resulting in lower recruitment and higher attrition rates. These difficulties seem to outweigh the benefits of a crossover study design (homogeneity between treatment groups and a smaller required sample size).

Recruitment of large numbers of patients can be challenging in pediatric research. In order to overcome this challenge, multicenter trials should be considered. Involvement of multiple centers may also increase generalizability of the findings.

A period of baseline assessment without treatment ("run-in period") is recommended. In order to adequately assess symptoms at baseline and to prevent bias due to concomitant medication usage, it is recommended that all trials start with a period of baseline assessment without treatment ("run-in period"). This committee suggests a run-in period of 2 weeks to permit adequate screening for eligibility at baseline. To minimize placebo effect, the sample size can be enriched by adding a 1-week placebo run-in phase excluding subjects who no longer meet inclusion criteria at the end of the run-in period. Although this lengthens study duration and adds to the complexity of the study design, it reduces the number of patients who may benefit from a possible placebo effect.

The study duration should be at least 8 weeks or more. The duration of a clinical trial for FC should be sufficient to monitor the efficacy of the investigated drug and to enable assessment of potential adverse effects. Longer trial durations are preferable, as a short trial duration may be insufficient to detect benefits, long-term effects and side-effects of the investigated drug. However, a lengthy trial duration may burden patients and their families and hinder recruitment and adherence to study-related activities such as keeping a daily bowel diary. This committee recommends that the duration of a trial should be at least 8 weeks.

In addition, it is recommended to have a treatment-free monitoring period after completion of the trial of at least 2 weeks to assess whether treatment effects are sustained after the intervention is discontinued. During this period, rescue medication should be allowed, as long as it is documented clearly and taken into account when evaluating treatment success during this period.

When investigating a novel drug that is not yet available commercially in a randomized, double-blind, placebo-controlled clinical trial,

all participants should be provided with the opportunity to continue in an open-label study after completing the randomized, double-blind, placebo-controlled clinical trial to enable access to a drug in development and to appraise longer term safety.

In order to assess long-term outcomes, this committee recommends an open-label treatment period with a duration of 12 months or more, following the randomized, double-blind, placebo-controlled clinical trial.

Bowel cleanout regimens prior to initiation of the trial should be clearly specified. The drug-free run-in period may result in worsening of symptoms and potentially lead to the formation of a fecal impaction. At the time of baseline assessment (following the run-in-period), subjects should be assessed for presence of a fecal impaction. If present, the fecal impaction should be removed before initiating the treatment phase of the study in order to avoid influencing the study results and to reduce baseline variability among patients. A bowel cleanout regimen can be prescribed for all study participants prior to initiation of the study regardless of the presence of fecal impaction, or children can be assessed individually to determine whether a bowel cleanout regimen is needed. This committee recommends a bowel cleanout regimen for all study participants, regardless of whether they are impacted, of at least 3 days, either with polyethylene glycol (1-1.5 g/kg/day) or with daily enemas. Polyethylene glycol and enemas are equally effective in the treatment of fecal impaction.[7,14] Following disimpaction, successful removal of the fecal mass should be confirmed. Evaluation of success of disimpaction should ideally be based on history and physical examination. However, how to perform the assessment of the efficacy of the disimpaction treatment should be at the discretion of the physician.

The use of rescue medication during the trial should be clearly specified in the study protocol. When a child does not defecate for 3 days during the trial, rescue medication should be offered to induce defecation. The type, dosage, and frequency of permitted rescue medications should be clearly specified and standardized in the study protocol and use of such medication needs to be documented throughout the study. Moreover, the use of rescue medication should be taken into account when assessing treatment outcome.

3 | RECOMMENDATIONS FOR PATIENT SELECTION

Selection of subjects should be based on the Rome IV criteria. In trials for FC in children, a careful history should be obtained to select patients who fulfill the Rome IV criteria for FC (Table 1).[15,16] In order to enhance the external validity of the trial, it is recommended to include subjects with a variety of demographic features (eg, age, ethnicity, race, and sex). If demographic variables are used for inclusion or exclusion, these should be documented clearly and any restriction of the study population must be justified.

Patient selection criteria should specify age and the acquisition of toilet training skills, as these are relevant in the selection of study outcomes. The acquisition of toilet training skills marks an important milestone in children. In the assessment of pediatric defecation disorders, the acquisition of toilet training skills also determines how children with defecation disorders are evaluated; the Rome IV criteria for FC differentiate between children who are toilet-trained and children who are not. In children who are not toilet-trained, stools are assessed in diapers instead of in the toilet, a factor which may affect the choice of stool scales used to appraise stool consistency.[17] Moreover, in children who are not toilet-trained, it would be inadequate to use fecal incontinence as an outcome measure. When designing a treatment trial, it is therefore important to consider whether including both groups of patients, those who are and those who are not toilet-trained, would be beneficial to the study design. Furthermore, a sub-analysis should be considered for each group.

Inclusion of children with major psychiatric disorders or a history of abuse may negatively impact treatment success rates in clinical trials and should therefore be avoided. Major psychiatric disorders such as bipolar disorder, schizophrenia, or major depression may affect treatment success in clinical trials and thus this committee recommends excluding children with these disorders from participating in clinical trials. Consideration should be given whether to exclude children who are known to have been physically or sexually abused, as these patients may be particularly refractory to treatment. Evaluation by a psychologist or psychiatrist could be considered to assess the patient's eligibility.

Physical examination with perianal inspection should always be performed in the diagnostic workup of children with constipation and a digital rectal examination is required for the diagnosis of FC in children who meet only one Rome IV criterion based on the medical

TABLE 1 Rome IV criteria for functional constipation for infants/toddlers and children/adolescents.[15,16]

Infants/toddlers
G7. Diagnostic Criteria for Functional Constipation
Must include 1 month of at least 2 of the following in infants up to 4 years of age: • 2 or fewer defecations per week • History of excessive stool retention • History of painful or hard bowel movements • History of large-diameter stools • Presence of a large fecal mass in the rectum In toilet-trained children, the following additional criteria may be used: • At least 1 episode/week of incontinence after the acquisition of toileting skills • History of large-diameter stools that may obstruct the toilet
Children/adolescents
H3a. Diagnostic Criteria for Functional Constipation
Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome: • 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years • At least 1 episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of large-diameter stools that can obstruct the toilet After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

TABLE 2 Recommended endpoints for pharmacological clinical trials in children with functional constipation

Primary endpoint: successful treatment	Not fulfilling the Rome IV criteria
Secondary endpoints based on core outcome set	Defecation frequency
	Stool consistency
	Painful defecation
	Quality of life
	Side-effects
	Fecal incontinence frequency[a]
	Abdominal pain[a]
	School absence[a]
Other secondary endpoints	Withholding behavior
	Large-diameter stools that obstruct the toilet[a]
	Large fecal mass in the rectum
	Use of rescue medication
	Patient/parent satisfaction

[a]If age appropriate.

history and abdominal examination. A physical examination should always be performed in the diagnostic workup of children with symptoms suspect for FC. This should include lumbosacral and perianal inspection. Physical examination may reveal alarm signs suggestive of organic causes of constipation or child abuse, which may exclude these children from participating in a trial. Lumbosacral inspection may reveal a dimple, tuft of hair, gluteal cleft deviation, sacral agenesis, or flat buttocks. Moreover, perianal inspection may uncover signs related to FC such as perianal feces, erythema, skin lesions, or anal fissures. Some of these findings may require specific treatment and may constitute a reason to exclude patients from the trials.

A digital rectal examination is not always required in the diagnostic workup of children with symptoms suspect for FC. If a child fulfills two or more of the Rome IV criteria based on the history, a digital rectal examination will not alter the diagnosis. However, a digital rectal examination can be necessary to establish a diagnosis of FC according to the Rome IV criteria in children who only fulfill one criterion based on the history.

The presence of fecal impaction at baseline and persistence of impaction after the cleanout should be evaluated and documented. Evaluation of the presence of fecal impaction should preferably be based on a digital rectal examination. However, the method of assessment of fecal impaction should be at the discretion of the physician.

Due to the lack of evidence for the use of abdominal X-rays in the assessment of FC and the associated radiation exposure,[18] this committee does not routinely recommend to perform a plain abdominal X-ray to assess potential fecal impaction. Occasionally, there may be patients in whom it is impossible to judge the presence of fecal impaction by physical examination (eg, extreme obesity). In these cases, a plain abdominal X-ray may be valuable.

4 | RECOMMENDED INCLUSION AND EXCLUSION CRITERIA

4.1 | Inclusion criteria

1. Patients fulfill the Rome IV criteria for FC
2. Patients are 0-18 years of age, more specific age ranges may apply
3. Patient and/or parents are able to read and comprehend questionnaires and complete diaries

4.2 | Exclusion criteria

1. Children with organic causes of constipation; eg, celiac disease, pediatric intestinal pseudo-obstruction, hypothyroidism, spina bifida, anorectal malformations, or Hirschsprung's disease
2. Significant chronic health conditions requiring specialty care (eg, urolithiasis, ureteropelvic junction obstruction, sickle cell, cerebral palsy, hepatic, hematopoietic, renal, endocrine, or metabolic diseases) that could potentially impact the child's ability to participate or confound the results of the study
3. Unintentional weight loss greater than or equal to 5% of their body weight within the last 3 months
4. Gastrointestinal blood loss
5. Recurrent or unexplained fevers
6. Pregnancy
7. History of abdominal surgery involving the luminal gastrointestinal tract, except appendectomy, or hernia repairs
8. Concomitant use of drugs that are known to affect gastrointestinal motility
9. History of hypersensitivity or allergy to the medication being tested
10. Established diagnoses of autism spectrum disorders
11. Major psychiatric disorders (bipolar disorder, schizophrenia, major depression)
12. Use of sacral nerve stimulation (SNS) or antegrade enemas through a cecostomy or an appendicostomy

4.3 | Optional exclusion criteria, based on potential negative impact on treatment success

13. History of physical or sexual abuse

5 | RECOMMENDATIONS FOR CONCURRENT USE OF MEDICATIONS OR THERAPIES

Prior to enrollment into the trial, all participants should receive education, information and reassurance as standard care for FC. Patients should receive the same education, information and reassurance as in regular clinical practice. These interventions have been shown to

improve chronic defecation problems and should therefore be similar in both study arms.[19] These interventions should be implemented prior to the run-in period and not during the trial period, to prevent confounding.

The use of concurrent medications that affect gastrointestinal motility should be carefully evaluated and may constitute a reason for exclusion if these drugs cannot be stopped. Drugs that may affect motility include (but are not restricted to): metoclopramide, erythromycin, bethanechol, amoxicillin/clavulanate, azithromycin, domperidone, amitriptyline, hyoscyamine, clonidine, baclofen, dicyclomine, and scopolamine.

During the trial, concomitant use of laxatives other than rescue medication should not be allowed except in "add-on" study designs. Laxatives other than the drug under investigation or rescue medication should only be allowed in an "add-on" study design, where one group receives standard treatment, while the other group receives standard treatment along with the drug that is under investigation. In other study designs, the confounding effect of using laxatives other than the intervention drug should be avoided. Other medications that the patient uses at the time of screening and that are not considered to affect gastrointestinal motility or interact with the investigational drug should be kept at a constant dose and schedule for the duration of the trial if medically possible or stopped before the patient is enrolled in the study. Concurrent medications should be taken during both the run-in period and the trial period in order to minimize the confounding effect of changes in these medications on study results. Concurrent medications need to be evaluated thoroughly to identify any interactions that could occur with the investigated drug.

Initiation of new drug treatments, complementary or alternative therapies during the study period should not be allowed. If the patient's medical status requires a new intervention or treatment, the impact of such changes should be evaluated thoroughly and it should be considered whether to withdraw the patient from participation in the trial.

Besides standard non-pharmacological interventions (education, scheduled toilet sits, and keeping a bowel diary), other non-pharmacological interventions aimed at treating FC should be avoided during the trial. Any non-pharmacological interventions implemented prior to or during the trial should be clearly documented. Non-pharmacological interventions such as education, behavioral interventions and keeping a bowel diary are of key importance in the initial treatment of FC and these interventions are therefore frequently implemented in children before they enter a trial. Before the run-in period, it is important to make sure that these interventions are similar for all patients.

In general, patients should be encouraged to meet the daily recommendations for fiber and fluid intake, but dietary interventions such as increasing fiber and fluid intake above the normal recommendations should be avoided during the study.

Over the past decades, the interest in pre-, pro-, and synbiotics has increased and some patients may use over the counter products. This should be carefully sought out, documented and, if necessary, these treatments should be stopped or could constitute a reason to reconsider the patient's eligibility for participation. If these participants are allowed to continue using these products, they should be kept at a stable dose.

Children with severe intractable FC are sometimes treated with antegrade continence enemas or SNS. In view of the severity of their constipation, these patients should be excluded from participation in clinical trials.

6 | RECOMMENDATIONS FOR DOCUMENTATION

Demographic information on patients entered and excluded (gender, age, race, ethnicity, site of enrollment), and reasons for exclusion, should be documented. In order to enable the assessment of the generalizability of study results and to assess the risk of selection bias, it is important that demographic features of included and excluded patients are clearly documented.

Withholding behavior may influence treatment success. Withholding behavior is one of the diagnostic Rome IV criteria for FC in children. This behavior is often initiated after a negative experience such as passage of a hard, painful or frightening bowel movement.[20] Stool withholding behavior can lead to fecal impaction, which may result in overflow fecal incontinence, the involuntary loss of soft stools that pass around the obstructing fecal mass. Withholding behavior may have a negative impact on treatment outcome.[21] Information on the presence of withholding behavior should therefore be clearly documented. Although not specifically recommended by this committee, it could be considered to use withholding behavior as a covariate or use this for balanced randomization.

If present, psychological comorbidity should be documented. The co-occurrence of behavioral disorders in children with functional defecation disorders has been well-described in the literature and may result in a less favorable treatment response.[22-24] If behavioral disorders (such as ADHD/ADD) are present, these conditions should therefore be documented at enrollment. As these disorders are highly prevalent among children with FC,[23,25] this committee does not recommend to exclude these children because this could result in an unrepresentative reflection of the true patient population.

The use of daily diaries is recommended. Daily diaries are recommended to collect data relevant to the study (eg, bowel movement frequency, fecal incontinence frequency, stool consistency, administration of study medication, and rescue medication). These diaries should preferably be in electronic form. In younger children, parents should fill out the diary, while in adolescents this can be done by the patients themselves. The younger the child, the more reliable symptom report by parents is, while in adolescents the parents may not be able to provide adequate information on the child's symptoms. Electronic diaries enable recording the date and time of completion of the questionnaire and reduce the risk of recall bias resulting from filling out the diary in hindsight. Daily diaries should also track whether study medication was taken as

prescribed and whether patients are adherent to treatment. Using a reminder on the electronic diary can help improve therapy adherence and adherence to study activities such as completing the daily diary.

All adverse events should be documented and reported as unexpected adverse events may occur during the course of the trial. Rules for cessation of the trial must be pre-established and documented in the study protocol. Adverse effects should be actively sought out. All adverse events should be documented and evaluated by an independent data and safety monitoring board (DSMB). For general guidelines, see: http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf.

Treatment allocation and randomization should be specified and documented a priori including the method of randomization and treatment allocation. Prior to initiation, trials should be registered in a public location (eg, https://www.clinicaltrialsregister.eu/). The results of the study should be published, regardless whether the results are positive, negative, or inconclusive. Sources of funding and any conflicts of interest need to be disclosed.

Reasons for withdrawal and the number of patients lost during the follow-up period should be documented. It is recommended to follow the CONSORT guidelines for RCTs and to provide a flow diagram depicting patient flow during the trial (http://www.consort-statement.org/).

If patients benefit from the investigated drug, they should be provided with the opportunity to continue using this medication after the trial ends. Agreements on continuation of the investigated drug after the trial ends should be clearly documented and communicated with the patients before initiation of the trial. Sponsors should commit to provide the drug free of cost to those patients who have shown to benefit from the drug until the drug costs are covered by the patient's insurance.

7 | RECOMMENDATIONS FOR ENDPOINTS

Endpoints should be based on patient reported outcomes when possible. In children 10 years of age and older, endpoints should be based on both patient-reported outcomes and proxy-reported outcomes (parents or caretakers). In younger children, mainly proxy-reported outcomes should be used. Even in children ≥10 years of age, some symptoms or outcomes related to FC may be difficult to assess and express for children. Moreover, the reliability of answers to questions that may be embarrassing to children may be questionable. On the other hand, parents may not be able to provide detailed information on their teenager's bowel habits. Therefore, it is useful to always base endpoints on both patient and proxy report in children ≥10 years of age when possible.

No validated endpoints are available for clinical trials in children with FC. This committee recommends using treatment success as primary outcome and suggests that the definition of treatment success should preferably be based on the Rome IV criteria. Using uniform endpoints enables comparison among different trials. Currently, primary endpoints used in clinical trials vary greatly among studies, a factor which makes it difficult to compare trial results.[12,13] Furthermore, up to now, there has been a major emphasis on using bowel movement frequency as primary outcome. As FC can be diagnosed in children even when they have a normal below movement (BM) frequency (≥3 BMs per week), this may be inadequate. Based on expert opinion and a consensus process, this committee recommends defining treatment success based on the Rome IV criteria. A child who fulfills the Rome IV criteria for FC prior to enrollment into a trial and does no longer fulfill the Rome IV criteria at the end of the trial period should be considered successfully treated. The diagnosis FC is established if the Rome criteria are fulfilled for a duration of 4 weeks. For the definition of treatment success, defined as not fulfilling Rome criteria for FC, this committee recommends that the child should fulfill less than 2 of the Rome criteria for FC during 3 of the last 4 weeks of the trial, including the last week. This committee agreed to use this definition of treatment success as primary endpoint, while acknowledging that symptom relief can occur without achieving successful treatment, which should be assessed through secondary endpoints.

Secondary endpoints of interest include: separate items of the Rome IV criteria, abdominal pain, quality of life, side-effects, and school absence. Recently, Kuizenga-Wessel et al. have published a core outcome set to be used in trials on childhood FC.[26] This core outcome set was developed using a Delphi questionnaire; healthcare providers, parents and children with FC were asked to list outcomes they considered relevant. After creation of a shortlist, these items were prioritized by healthcare providers, parents and children with FC, resulting in a selection of items considered most relevant in the assessment of treatment outcome during clinical trials. This pediatric core outcome set for FC involves the following items: defecation frequency, stool consistency, painful defecation, fecal incontinence frequency, quality of life, side-effects, and school absence. Moreover, the need to use rescue medication can be considered as an endpoint. It should also be considered to include an endpoint related to patient or parent satisfaction with treatment. Table 2 provides an overview of suggested secondary endpoints.

For the assessment of defecation frequency, it is important to differentiate between "spontaneous" bowel movements and bowel movements induced by administration of rescue medication. A defecation frequency of 2 or less per week is one of the Rome IV criteria for FC in children and this cutoff value is often used in clinical trials to define successful treatment. One of the difficulties in the evaluation of defecation frequency is related to the use of rescue medication in clinical trials. A BM that occurs after rescue medication should not be included as a measure of BM frequency for the drug that is being tested. The committee proposes to use the concept of using spontaneous BM (SBM), which is defined as a BM not produced by the use of rescue medication. BMs that occur within 24 hours after administration of the rescue medication are not to be considered spontaneous.

Another difficulty in the assessment of bowel movements arises when children defecate but are unable to completely evacuate the stools at an initial attempt and return to the toilet within a short amount of time for a subsequent bowel movement. If these two bowel movements are considered separately, this may result in an overestimation of the defecation frequency which may bias study results. This committee recommends that two bowel movements occurring within one hour should be considered as one bowel movement. Furthermore, clear instructions should be given on how to evaluate episodes of fecal incontinence. These should not be regarded as bowel movements, because this may result in an overestimation of the bowel movement frequency.

Assessment of stool consistency should rely on stool form scales. Assessment of stool consistency in children can prove to be challenging. A commonly used tool in the evaluation of stool consistency is the Bristol Stool Scale, which was developed by Lewis and Heaton in 1997 (figure 1).[27] This scale involves 7 types of stools, ranging from hard to soft stools. Although this scale is frequently used in children of all ages, it can be debated whether this stool form scale is appropriate to be used in children who are not toilet-trained and in whom stool consistency is assessed in diapers. To support this criticism, a recent study on the agreement between parental report of stool consistency and the Bristol Stool Scale in children under 4 years of age showed poor agreement between the two methods.[28] For that reason, a stool form scale specific for infants has been developed, which allows assessment of stool consistency based on images of stools in diapers, but this scale is not commonly used in research yet.[17,29] The original Bristol Stool Form Scale (BSFS) has also been modified for children; the authors of this modified scale reduced the number of types of stools on the chart from 7 to 5, omitting types 3 and 5 from the original Bristol Stool Scale.[30,31] Currently, the original Bristol Stool Scale remains the most frequently used scale in adults and recent recommendations for clinical trials in children with irritable bowel syndrome have also recommended the use of the original 7-item Bristol Stool Scale by Lewis & Heaton for research purposes. This committee recommends using the original Bristol Stool Scale for the assessment of stool consistency in FC trials in children who are toilet-trained. In children who are not toilet-trained, stool consistency assessment with the Bristol Stool Scale may, however, not be reliable. Assessment of stool consistency should occur as soon as possible after a bowel movement to minimize the risk of recall bias.

The complexity of the outcomes studied should fit the developmental age of the child. In adult research, symptoms such as feelings of incomplete evacuation and straining are often taken into account in the assessment of treatment outcome. However, these endpoints used in adults are difficult to assess in young children. In young children, withholding behavior can easily be mistaken for straining and children may have difficulties to reliably express whether they have evacuated their stools completely. Outcomes that are likely difficult to assess in the age group under investigation should therefore be avoided.

8 | SAFETY ASSESSMENT

Safety assessment of novel therapeutic agents should be an important part of clinical trials. This includes detailed assessment of adverse events. Safety assessment should also be tailored to the mechanism of action of the investigated drug and any adverse events or interactions that may be expected to occur.

It could also be considered to assess palatability and the ability of children to ingest the investigated drug. These items, although not directly related to efficacy, may prove to be important to assess clinical applicability of new drugs, especially in children.

9 | DATA ANALYSIS

Performing a sample size calculation prior to initiation of the study is required and assumptions for this calculation should be documented. Clinical trials for childhood FC often lack a sample size calculation or a detailed description of the assumptions used to calculate this sample size. Across placebo-controlled trials in children with FC, high placebo response rates have been reported, ranging from 18% to 42%.[32-34] This should be taken into account when calculating the sample size; due to the small difference between the effect in the intervention group compared to the placebo group, a large sample size is required. This will be even larger if there are more than 2 arms in the study.

Data analysis should focus on differences between patients in each treatment arm based on pre-established, clinically relevant definitions of treatment response. Data should be analyzed using an intention-to-treat (ITT) principle, in which data from all enrolled patients are analyzed based on initial treatment assignment regardless of their completion of the trial or compliance with the protocol. A per-protocol analysis could be considered as a secondary analysis. Missing data are best managed using appropriate imputation procedures.

It is not recommended to perform interim analyses, as these may result in misleading or inaccurate observations. This does not apply for DSMB requirements.

10 | COMMENTARY

These recommendations are based on evidence when possible and expert opinion in cases of insufficient evidence. Some of the major recommendations focus on study design, inclusion/exclusion criteria, required diagnostic workup, trial duration, efficacy endpoints, and outcome measures for clinical trials on FC in children. The aim of these recommendations is to provide standardization for clinical trials in FC in children.

This committee recommends conducting multicenter, randomized, double-blind, placebo-controlled, parallel-group, clinical trials and the analysis of data should be based on an ITT principle. It is recommended to assess patient-reported outcomes whenever possible and to use the Rome IV criteria as inclusion criteria. No longer meeting the Rome IV criteria at the end of the trial for FC was thought to be the

optimal definition of treatment success for clinical trials in children. The use of this primary endpoint moves us apart from adult studies and previous clinical trials in children that commonly used number of SBM as primary endpoint.[32,34-36] The decision did not come without discussion due to the lack of data that result from the novelty of this approach and validation studies for this proposed primary endpoint are needed. Establishing an increase in number of stools from baseline as a sole primary efficacy endpoint, although objective and easy to assess, was believed to reduce constipation to a single item that does not represent all the core outcomes that impact children with FC and their families.

The pathophysiology of constipation in children differs from adults. Withholding is the most common cause of constipation in children, often occurring after a painful defecation experience. Children who receive laxatives may have an increased number of bowel movements, but may still have hard stools, painful defecation, abdominal pain, and episodes of fecal incontinence. Thus, considering an increase in bowel movements alone to be representative of a successful treatment, is too simplistic as it does not include some of the most bothersome symptoms for the child and family.[26] In contrast to clinical trials in adults with FC, the use of number of spontaneous bowel movements as primary efficacy endpoint has resulted in negative clinical trials in children. A pediatric clinical trial on a novel serotonergic agent that used a combination of ≥3 bowel movements weekly and ≤1 episode of fecal incontinence per 2 weeks as primary efficacy endpoints did not show a beneficial effect compared with placebo while the trial was positive when conducted in adult subjects.[32] The primary endpoint of the pediatric trial also included episodes of fecal incontinence, which was not the case in the adult study. The investigated drug significantly increased the number of bowel movements in adults (secondary endpoint) while there was no significant difference between drug and placebo in the improvement of the number of spontaneous bowel movements from baseline in the pediatric trial. Studies in children with constipation also differ from studies conducted in adults regarding the rate of efficacy of the placebo arm, which is higher in children. In a previous pediatric study on a serotonergic agent, there was improvement in the number of bowel movements in both children and adults, but due to the higher placebo effect in children it failed to achieve statistical significance in the pediatric study.[32] A high placebo effect was also found for the number of episodes of fecal incontinence.

This committee recommends to include secondary endpoints that were found to be relevant to children, parents, and healthcare professionals in a recent study.[26] Furthermore, the committee recommends using the BSFS to assess the consistency of the child's stools. There is little evidence on validation of the BSFS in children. Studies among parents[28] and children[37] have shown that the perceived consistency of the bowel movement does not always match the appropriate category of the BSFS. Despite the lack of validation of the BSFS in children and until new scales with proven validity are developed, there was agreement on using the BSFS due to its familiarity, easy availability and to harmonize with the recommendations on clinical trials for IBS issued by our committee.[38] As the criterion on hard stools in the Rome IV criteria is not isolated and is expressed as a history of hard or painful stools, low accuracy in establishing stool consistency was considered not to be as relevant as some of the other Rome IV criteria. This was demonstrated in studies that showed that the prevalence of constipation in children using the Rome III criteria was not affected by the potential limitations of determining stool consistency using the BSFS.[28,37]

Although the presence of a large fecal mass in the rectum is a criterion of the Rome IV criteria, the committee did not mandate to conduct a rectal examination in all cases. Instead, digital rectal examination is required for the diagnosis of FC in the case of children who meet only one Rome IV criterion after a thorough medical history and careful abdominal examination, this is in agreement with the most recent guidelines for the evaluation and management of FC.[7]

Constipation is common in children with psychological comorbidities. Excluding children with all psychological comorbidities would make recruitment challenging and would limit the external validity of the clinical trial. However, this committee recommends excluding children with major psychiatric disorders and a known history of abuse.

11 | FUTURE RECOMMENDATIONS

The scientific field of pediatric gastroenterology related to childhood FC is rapidly evolving. Novel therapeutic drugs (eg, prucalopride, lubiprostone, linaclotide) have been shown to be effective in adult patients with FC and trials in children are either recently completed or still ongoing. Moreover, new non-pharmacological treatment options involving electrical stimulation (ie, SNS, percutaneous tibial nerve stimulation, transcutaneous electrical nerve stimulation) have received increased interest and are likely to be studied more extensively in trials in the near future. Advances in technology have led to a steep increase in information that can be obtained through diagnostic interventions such as manometry testing, which may eventually result in better patient characterization. A better patient characterization will result in more adequate patient selection for specific treatment options—enabling a tailored treatment approach. Aside from taking the abovementioned recommendations into account, future pharmacological trials should aim to provide detailed information about study drug characteristics and patient characteristics in order to allow the development of such tailored treatment strategies.

12 | SUMMARY

General recommendations for clinical trials of FC in children:

12.1 | Design

- The recommended study design is a multicenter randomized, double-blind, placebo-controlled, parallel-group, clinical trial.
- A treatment-free run-in period of 2 weeks is recommended.
- A bowel cleanout should be performed in all study participants before the start of the active trial.
- The study duration should be at least 8 weeks.
- Inclusion criteria should be based on the Rome IV criteria.

- Endpoints should be based on patient reported outcomes when possible.
- The definition of treatment success should be based on the Rome IV criteria.
- It is recommended to include the following secondary endpoints (if applicable to the patient population): defecation frequency, stool consistency, painful defecation, quality of life, side-effects, fecal incontinence, and school absence.
- The use of daily (electronic) diaries is recommended.
- Results should be evaluated according to an ITT principle.
- All study participants should receive education, information, and reassurance as standard care for FC prior to initiation of the trial to avoid confounding.
- Assessment of stool characteristics should be done as soon as possible after the bowel movement has occurred and should be based on the BSFS in children who are toilet-trained.

12.2 | Documentation

- Demographic information on patients included and excluded and reasons for exclusion should be documented.
- Demographic and clinical characteristics of the subjects in the treatment group and the placebo group should be documented.
- All adverse events should be documented, reported, and evaluated by a DSMB.
- Rules for cessation of the study should be documented in the study protocol.
- Methods for treatment allocation and randomization should be documented in the study protocol.
- A sample size calculation should be performed prior to initiation of the trial and assumptions used to determine this sample size should be specified.
- Trials should be registered and made publicly accessible.
- Withdrawal from the study, reasons for withdrawal and loss to follow-up should be documented.
- Results should be reported according to the CONSORT guidelines.
- The results of the study should be published regardless whether the results are positive, negative, or inconclusive.
- All sources of funding and any potential conflicts of interest should be disclosed.

CONFLICTS OF INTEREST

S. Nurko, M. Saps, C. Di Lorenzo and M.A. Benninga were part of the pediatric working committees of the Rome Foundation and have developed the Rome IV criteria discussed in this review. M. Saps is the Chair of the Committee on Pediatric Clinical Trials of the Rome Foundation. M. Saps is a scientific consultant for Sucampo, Forest, Quintiles, Ardelyx, QOL Medical, IMHealth Science, Nutricia. C. Di Lorenzo is a scientific consultant QOL Medical, IMHealth Science, Sucampo, Merck, Nestlé. M.A. Benninga is a scientific consultant for Shire, Sucampo, Astrazeneca, Norgine, Zeria, Coloplast, Danone, Friesland Campina, Sensus, Novalac. S. Nurko is a consultant for Sucampo, Theravance. The authors report no other relevant potential conflicts of interest. This document reflects J.A.J.M. Taminiau's personal opinion and not necessarily the Agency's views.

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REFERENCES

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol*. 2011;25:3-18.
2. Koppen IJN, Lammers LA, Benninga MA, Tabbers MM. Management of functional constipation in children: therapy in practice. *Paediatr Drugs*. 2015;17:349-360.
3. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Clinical practice: diagnosis and treatment of functional constipation. *Eur J Pediatr*. 2011;170:955-963.
4. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, Grootenhuis MA, Derkx BH, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. *Arch Dis Child*. 2004;89:1124-1127.
5. Bongers MEJ, Benninga MA, Maurice-Stam H, Grootenhuis MA. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. *Health Qual Life Outcomes*. 2009;7:20.
6. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. *J Pediatr*. 2009;154:258-262.
7. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58:258-274.
8. Gordon M, Naidoo K, Akobeng AK, Thomas AG. Cochrane Review: osmotic and stimulant laxatives for the management of childhood constipation (Review). *Evid Based Child Health*. 2013;8:57-109.
9. Michaud L, Lamblin M-D, Mairesse S, Turck D, Gottrand F. Outcome of functional constipation in childhood: a 10-year follow-up study. *Clin Pediatr (Phila)*. 2009;48:26-31.
10. van Ginkel R, Reitsma JB, Büller HA, et al. Childhood constipation: longitudinal follow-up beyond puberty. *Gastroenterology*. 2003;125:357-363.
11. Bongers MEJ, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics*. 2010;126:e156-e162.
12. Kuizenga-Wessel S, Benninga MA, Tabbers MM. Reporting outcome measures of functional constipation in children from 0 to 4 years of age. *J Pediatr Gastroenterol Nutr*. 2015;60:446-456.
13. Kuizenga-Wessel S, Heckert SL, Tros W, van Etten-Jamaludin FS, Benninga MA, Tabbers MM. Reporting on outcome measures of functional constipation in children - a systematic review. *J Pediatr Gastroenterol Nutr*. 2016;62:840-846.
14. Bekkali N-L-H, van den Berg M-M, Dijkgraaf MGW, et al. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics*. 2009;124:e1108-e1115.

15. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150:1443-1455.
16. Hyams JSS, Di Lorenzo C, Saps M, Shulman RJJ, Staiano A, van Tilburg M. Functional disorders: children and adolescents. *Gastroenterology*. 2016;150:1456-1468.
17. Ghanma A, Puttemans K, Deneyer M, Benninga MA, Vandenplas Y. Amsterdam infant stool scale is more useful for assessing children who have not been toilet trained than Bristol stool scale. *Acta Paediatr*. 2014;103:e91-e92.
18. Benninga MA, Tabbers MM, van Rijn RR. How to use a plain abdominal radiograph in children with functional defecation disorders. *Arch Dis Child Educ Pract Ed*. 2016;101:187-193.
19. van der Plas RN, Benninga MA, Taminiau JA, Büller HA. Treatment of defaecation problems in children: the role of education, demystification and toilet training. *Eur J Pediatr*. 1997;156:689-692.
20. Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. *Nat Rev Gastroenterol Hepatol*. 2011;8:502-511.
21. Nurko S, Saps M. Treating constipation with prucalopride: one size does not fit all. *Gastroenterology*. 2014;147:1214-1216.
22. van Dijk M, Benninga MA, Grootenhuis MA, Last BF. Prevalence and associated clinical characteristics of behavior problems in constipated children. *Pediatrics*. 2010;125:e309-e317.
23. McKeown C, Hisle-Gorman E, Eide M, Gorman GH, Nylund CM. Association of constipation and fecal incontinence with attention-deficit/hyperactivity disorder. *Pediatrics*. 2013;132:e1210-e1215.
24. Joinson C, Heron J, Butler U, von Gontard A. Psychological differences between children with and without soiling problems. *Pediatrics*. 2006;117:1575-1584.
25. Kuizenga-Wessel S, Koppen IJN, Vriesman MH, et al. Attention deficit hyperactivity disorder and functional defecation disorders in children. *J Pediatr Gastroenterol Nutr*. 2017;1. https://doi.org/10.1097/MPG.0000000000001695.
26. Kuizenga-Wessel S, Steutel NF, Benninga MA, et al. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. *BMJ Paediatr Open*. 2017;1:e000017.
27. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-924.
28. Koppen IJN, Velasco-Benitez CA, Benninga MA, Di Lorenzo C, Saps M. Using the Bristol Stool Scale and parental report of stool consistency as part of the Rome III criteria for functional constipation in infants and toddlers. *J Pediatr*. 2016;177:44-48.e1.
29. Bekkali N, Hamers SL, Reitsma JB, Van Toledo L, Benninga MA. Infant stool form scale: development and results. *J Pediatr*. 2009;154:521-526.e1.
30. Chumpitazi BP, Lane MM, Czyzewski DI, Weidler EM, Swank PR, Shulman RJ. Creation and initial evaluation of a Stool Form Scale for children. *J Pediatr*. 2010;157:594-597.
31. Lane MM, Czyzewski DI, Chumpitazi BP, Shulman RJ. Reliability and validity of a modified Bristol Stool Form Scale for children. *J Pediatr*. 2011;159:437-441.e1.
32. Mugie SM, Korczowski B, Bodi P, et al. Prucalopride is no more effective than placebo for children with functional constipation. *Gastroenterology*. 2014;147:1285-95.e1.
33. Thomson MA, Jenkins HR, Bisset WM, et al. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. *Arch Dis Child*. 2007;92:996-1000.
34. Nurko S, Youssef NN, Sabri M, et al. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. *J Pediatr*. 2008;153:254-261, 261.e1.
35. Camilleri M, Piessevaux H, Yiannakou Y, et al. Efficacy and safety of prucalopride in chronic constipation: an integrated analysis of six randomized, controlled clinical trials. *Dig Dis Sci*. 2016;61:2357-2372.
36. Nelson AD, Camilleri M, Chirapongsathorn S, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. *Gut*. 2017;66:1611-1622.
37. Vriesman MH, Velasco-Benítez CA, Ramirez CR, Benninga MA, Di Lorenzo C, Saps M. Assessing children's report of stool consistency: the agreement between the pediatric Rome III questionnaire and the Bristol Stool Scale. *J Pediatr*. 2017;190:69-73.
38. Saps M, van Tilburg MAL, Lavigne JV, et al. Recommendations for pharmacological clinical trials in children with irritable bowel syndrome: the Rome foundation pediatric subcommittee on clinical trials. *Neurogastroenterol Motil*. 2016;28:1619-1631.

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