Neurogastroenterology & Motility

Neurogastroenterol Motil (2016) doi: 10.1111/nmo.12896

REVIEW ARTICLE

Recommendations for pharmacological clinical trials in children with irritable bowel syndrome: the Rome foundation pediatric subcommittee on clinical trials

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Key Points

- The Rome Foundation subcommittee for Pharmacological Clinical Trials in Children with IBS recommends randomized, double-blind, placebo-controlled, parallel-group, clinical trials to assess the efficacy of new drugs.
- Entry criteria for abdominal pain are a weekly average of worst abdominal pain in past 24 h of at least 3.0 on a 0–10 point scale or at least 30 mm in 100 mm Visual Analog Scale and for stool endpoints an average stool consistency of lower than 3 in the Bristol Stool Form Scale (BSFS) during the run-in period for clinical trials on IBS-C and an average stool consistency of greater than 5 in the BSFS during the run-in period for clinical trials on IBS-D.
- The endpoints for abdominal pain are a decrease in intensity of at least 30% compared with baseline and to meet or exceed the Reliable Change Index (RCI) for the sample.
- Changes in stool consistency are the primary endpoints for both, IBS with diarrhea (IBS-D) and IBS with constipation (IBS-C) in children.

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#The opinion is the personal view of the author and does not represent the agency's position.
Received: 10 February 2016
Accepted for publication: 30 May 2016

Abstract

Background *There is little published evidence of efficacy for the most commonly used treatments. Thus, there is an urgent need to conduct clinical trials on existing and novel therapies.* ***Purpose*** *In order to address these issues the Rome Foundation and members of the Pediatric Committee of the European Medicines Agency formed a subcommittee on clinical trials to develop guidelines for the design of clinical*

trials in children with irritable bowel syndrome (IBS). The following recommendations are based on evidence from published data when available and expert opinion. ***Key recommendations*** *The subcommittee recommends randomized, double-blind, placebo-controlled, parallel-group, clinical trials to assess the efficacy of new drugs. The combined endpoints for abdominal pain are a decrease in intensity of at least 30% compared with baseline and to meet or exceed the Reliable Change Index (RCI) for the sample. Stool consistency is measured with the Bristol Stool Scale Form (BSFS). The subcommittee recommends as entry criteria for abdominal pain a weekly average of worst abdominal pain in past 24 h of at least 3.0 on a 0–10 point scale or at least 30 mm in 100 mm Visual Analog Scale. For stool endpoints the committee recommends an average stool consistency lower than 3 in the BSFS during the run-in period for clinical trials on IBS-C and an average stool consistency greater than 5 in the BSFS during the run-in period for clinical trials on IBS-D. Changes in stool consistency are the primary endpoints for both IBS with diarrhea (IBS-D) and IBS with constipation (IBS-C).*

Keywords *abdominal pain, children, clinical trials, endpoints, irritable bowel syndrome, stool consistency.*

INTRODUCTION

Chronic abdominal pain is one of the symptoms most commonly encountered by pediatric providers and gastroenterologists. Abdominal pain or discomfort is the hallmark of functional abdominal pain disorders (FAPDs), conditions which include irritable bowel syndrome (IBS), functional dyspepsia (FD), functional abdominal pain – not otherwise specified (FAP-NOS) and abdominal migraine. The development of pharmacological therapies for these disorders in both adults and children has been limited by several factors, such as the incomplete understanding of their peripheral and central pathophysiological mechanisms, the lack of actionable biomarkers, the heterogeneity of these disorders and the major discrepancies in the methodologies and endpoints used in clinical trials. Thus, it is not surprising that here are currently no approved drugs for the treatment of FAPDs in children and there is little published evidence of efficacy for the most commonly used treatments. Only a few, small, randomized clinical trials have evaluated the effect of pharmacological interventions in the treatment of FAPDs in children[1] and thus, there is an urgent need to conduct clinical trials on existing and novel therapies.

Most drug clinical trials in adult patients with IBS[2–15] and some of the largest trials on FAPDs in children[16] have used global outcomes measures. In April 2009, the US Foods and Drug Administration (FDA) proposed the use of provisional primary endpoints for clinical trials in adults with IBS in place of global outcome measures. A guideline recommending the use of co-primary endpoints, assessing two major aspects of IBS – abnormal defecation and abdominal pain – was published by the FDA in 2012.[17] The use of these co-primary endpoints was subsequently also adopted by the European Medicines Agency (EMA) in 2013.[18] It remains unclear whether these recommendations are adequate for studies in children.[19] Specific considerations in the pediatric population frequently preclude using the same methodology in adults and children. Developmental and cognitive limitations and differences in clinical relevance between adults and children make some adult endpoints poorly applicable to children. Different symptom scales are validated in children of different age. Parents are also often hesitant to enroll their children in lengthy randomized trials that include a placebo arm.

In order to address these issues, the Rome Foundation and members of the Pediatric Committee of the European Medicines Agency formed a subcommittee on clinical trials that was charged with developing guidelines for the design of pediatric clinical trials in children with IBS. This subcommittee conducted a comprehensive review of the English scientific literature on clinical trials in functional gastrointestinal disorders (FGIDs) and pediatric chronic pain scales and stool scales. In addition, the subcommittee sought to identify gaps in knowledge about pediatric pain and stool scales to outline the future research agenda. The following recommendations are based on evidence from published data when available and expert opinion. The subcommittee considered that there was insufficient data to provide recommendations that could be based exclusively on high level of evidence. Therefore, the recommendations issued by this subcommittee could potentially be modified in future editions as new data become available.

RECOMMENDATION

Recommendations for Study Design

The goal of a clinical trial is to assess the safety and efficacy of an intervention to relieve or decrease the severity of the child's symptoms, to reduce the impact

of the disorders on the child's life and to improve the quality of life of the patient. Existing drug trials in FAPDs in children have used a wide variety of study designs, length of treatment, definitions, outcomes and measures. Disparities among studies make it difficult to compare results and combine data for meta-analysis.

Randomized, double-blind, placebo-controlled, parallel-group, clinical trials are recommended to assess the efficacy of new drugs. Pharmacological therapy for FAPDs in children has been associated with high placebo response rates that can range from a nocebo effect to more than 50% in some studies.[20] Therefore, double-blind, randomized, placebo-controlled, parallel group clinical trials are recommended to assess the efficacy of new drugs. Parallel design in which each study participant is randomly assigned to a group (intervention or placebo) with all the participants in each group receiving or not receiving the intervention is recommended. Parallel design avoids possible 'order' effects in which the effect or side effects of a drug could affect the outcome and possible 'carry-over' effects of crossover trials. Although the 'carry-over' effects could be minimized by a prolonged 'wash-out' period between treatments, this would prolong the length of the trial and result in lower recruitment and higher attrition rates. These challenges outweigh the benefits of crossover design which include avoiding possible imbalances between groups and needing a lower sample size. A common challenge in conducting randomized controlled trials (RCT) in children is successful recruitment of large number of patients. In order to overcome this challenge, multicenter trials should be considered.

A period of baseline assessment without treatment ('run-in period') is recommended. It is recommended that all trials start with a period of baseline assessment without treatment ('run-in period'). A run-in period of at least 1 week (preferably 2 weeks) is suggested to help screen out ineligible participants and provide objective baseline information.

Study duration should be of at least 4 weeks (preferably 6 weeks or more). The duration of the trial to best assess efficacy of a treatment was a topic of much debate within the working group. The duration should be sufficient to not only adequately address the outcome being measured, but also potential side effects or adverse reactions that could result from the therapy. It should also not be so long that children and their families become overburdened. Longer trial periods may also limit recruitment, a very common problem in pediatric clinical trials. It is recommended that the study duration should be at least 4 weeks (preferably 6 weeks or more). Duration of the trial should be based on the pharmacology of the compound. As a general rule, treatment periods shorter than 4 weeks are not recommended due to the variable course of IBS with periods of 'waxes and wanes'. A monitored treatment free period at the end of the trial is recommended to assess whether beneficial effects are maintained once the intervention is discontinued.

Recommendations for Patient Selection

Selection of subjects should best reflect the population that is affected. Demographic variables of patients included or excluded from the trial should be documented and the criteria for restricting the study population must be justified. Recruitment of subjects with broad demographic features is advisable. This includes different age, ethnicity, race, and gender. Enrolling subjects with varied degrees of pain intensity/duration and bowel symptoms is important in order to have a wide representation of the disorder in the community and because of common non-treatment effects in RCT such as regression to the mean, ceiling and bottom effects. **Enrolling children who meet Rome criteria but have mild average pain is discouraged** (e.g., <3.0 on a 10-point numerical pain intensity scale or <30 mm in 100 mm Visual Analog Scale [VAS]) since such a low baseline score may not be sufficient to demonstrate clinically meaningful improvement.[21]

It is best to identify different forms of FAPDs, such as IBS and FAP-NOS (functional dyspepsia is not covered in this guidelines), and perform trials only on those patients. As signs and symptoms of constipation predominant IBS (IBS-C) and diarrhea predominant IBS (IBS-D) differ, each type of disorder should be studied in separate clinical trials. The pediatric Rome IV committees have defined for the first time diagnostic criteria for IBS-C and IBS-D (Table 1). It is recommended to include specific IBS sub-types, such that IBS-C and IBS-D patients are only studied with pharmacological treatments appropriate to their subtype.

The general recommendation is to enroll children 8 years of age or older for the purpose of clinical trials, as most self-report measures are approved at this age. As there is little agreement between parent and child report of symptoms[22] the committee recommends that child report should be used for children ages 8 years old and above or up to the lowest age for which the pain scale has been validated. When enrolling children that are younger than 8 years of age, proxy report (parent or caretaker) may be required based on the validated questionnaire that is used.

Table 1 Rome criteria IV – irritable bowel syndrome (IBS) – IBS-C and IBS-D Subtypes

IBS with predominant constipation (IBS-C): >¼ (25%) of bowel movements with Bristol stool types 1 or 2 and <¼ (25%) bowel movements with Bristol stool types 6 or 7
IBS with predominant diarrhea (IBS-D): >¼ (25%) of bowel movements with Bristol stool types 6 or 7 and <¼ (25%) bowel movements with Bristol stool types 1 or 2

IBS, irritable bowel syndrome. Based on the Bristol Stool Form Scale (BSFS).[21]

Prior to the entry into the trial, all participants should receive education, information and reassurance as standard care for IBS. With the exception of necessary aspects inherent to the protocol such as contacting patient, follow up visits, documentation and possible workup, normal practice of care should not be modified and patients should be managed following normal clinical practice.

A careful history should be obtained to select patients that fulfill the criteria established by the Rome IV criteria for IBS. The Rome criteria have been widely accepted and used in RCT of children with FGIDs. While there is evidence of the construct validity of the Rome III criteria,[23,24] there is also conflicting evidence on the reliability of these criteria.[25,26] The Rome III criteria were found to be sensitive but their specificity has been put into question.[27] No validation studies have been yet published on the new version of the criteria (Rome IV), although studies are currently being conducted. In addition to fulfilling the Rome criteria, the inclusion criteria should also include a focused history and diagnostic work-up. Alarm symptoms should be identified to rule out other disorders that can mimic IBS.[27–29]

Required laboratory, imaging and endoscopic testing should be specified prior to the initiation of the trial. At a minimum, the work-up in children who present with abdominal pain should include blood count, CRP, anti-tissue transglutaminase antibody, IgA and determination of occult blood in stool and fecal calprotectin and/or lactoferrin. Children with diarrhea should also undergo stool culture and determination of ova and parasites. Abnormal laboratory tests or the presence of alarm features should prompt further investigation even when meeting Rome criteria for IBS. In addition, it is advisable to document any known history of comorbid psychological disorders and the presence of additional gastrointestinal symptoms, as these factors may influence treatment outcomes.

Similar principles should be applied to children with a diagnosis of 'functional abdominal pain-not otherwise specified' (NOS) (FAP-NOS) according to the Rome IV criteria. This group of children should use similar inclusion/exclusion criteria, trial design and workup with the exception of the aspects that are not pertinent to the diagnosis (changes in stool characteristics).

The recommended inclusion and exclusion criteria are summarized below.

Inclusion criteria

1 Satisfy Rome IV criteria (IBS-C, IBS-D or FAP-NOS).
2 Patient ages 8–18 years (lower ages can be considered if appropriate measures for are available).
3 Patient and parent ability to read and comprehend questionnaires.
4 Average daily pain rate of at least 3 out of 10 (numerical rating scale, NRS) or at least 30 mm in a 100 mm VAS met during a run-in period of at least 1 week (or similar cut off if a different validated pain scale is used for the study).

Exclusion criteria

1 Children who tested positive for bacterial or parasites infections.
2 Carbohydrate malabsorption, diagnosed either clinically (2 weeks exclusion diet with resolution of symptoms) or with proper testing (breath test,[30]). Children with carbohydrate intolerance who continue to have IBS symptoms while on an exclusion diet can still be included.
3 Children with chronic gastrointestinal disorders that mimic FAPDs: inflammatory bowel disease, pancreatitis, chronic liver disease, eosinophilic esophagitis, peptic ulcer disease, celiac disease, pseudo-obstruction, small bowel bacterial overgrowth, or Hirschsprung's disease.
4 Significant chronic health condition requiring specialty care (e.g., lithiasis, 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.
5 Unintentional weight loss greater than or equal to 5% of their body weight within the last 3 months.
6 Decreased growth velocity.
7 Gastrointestinal blood loss.
8 Recurrent or unexplained fevers.
9 Pregnancy.
10 Developmental disabilities impairing ability to understand or communicate.
11 History of hypersensitivity or allergy to medication being tested.
12 History of previous abdominal surgeries in the past 3 months.
13 Rome IV criteria diagnosis of functional constipation.

Recommendations for Concurrent Use of Medications or Therapies

The use of concurrent medications that affect pain sensitivity or psychiatric disorders should be carefully evaluated. Patients using drugs that affect intestinal function or pain sensation should generally be excluded. Patients on other medications at the time of screening should be encouraged to maintain a constant dose and schedule during the entire trial if medically possible. Concurrent medication(s) should be taken during the run in period in order to assess the effect on the baseline measures. Consideration should be given to the mechanism of action of the drug being studied and interference with metabolism of other drugs that may mask or potentiate the effect of drug being studied. Patients undergoing specific diets can be included provided no changes in diet are expected within the study period. Subjects should not start any new medications, complementary or alternative therapies during the study period. If the patient's status requires a new intervention or treatment, researchers should evaluate the impact of such changes and consider stopping participation in the current trial if ethically appropriate.

Recommendations for Documentation

Demographic information on patients entered and excluded (gender, age, race, ethnicity, site of enrollment), and reasons for exclusion, should be documented. We recommend the inclusion of children with a single functional gastrointestinal diagnosis. However, if children with co-existence of two diagnoses are included in the study the presence of both should be documented as the outcome of this subset of patients may differ from those with a single diagnosis. Similarly, we recommend documenting the presence of extra-intestinal somatic complaints.

When available, psychological disturbances should be evaluated and the information documented. Psychological comorbidities could influence the outcome resulting in more or less favorable treatment response.[31,32]

The use of daily diaries is recommended. Daily diaries should include relevant study data preferably in electronic form. The use of daily diaries, when possible with reminder alarms, helps minimize recall bias[25]and records the date and time of completion of the questionnaire.

All adverse events should be documented and reported as unexpected adverse events may occur during the course of the trial. **Stopping rules have to be pre-established** and documented in the study protocol. All adverse events should be evaluated by an independent data and safety monitoring board (DSMB). For general guidelines see: https://www.nichd.nih.gov/health/clinicalresearch/clinical-researchers/steps/Pages/conduct_monitor.aspx; http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf.

Treatment allocation and randomization should be specified and documented *a priori* including method of random allocation sequence and type of randomization. Prior to initiation, trials should be registered in a public location (i.e. https://clinicaltrials.gov/; https://www.clinicaltrialsregister.eu/). The results of the study should be published even if the results of the trial are negative or inconclusive. Sources of funding and conflicts of interest of each investigator should be disclosed.

Recommendations for Primary Endpoints

Primary endpoints should be based on patient reported outcomes (PROs) when possible. Primary endpoints should be based on patient reported outcomes (PROs) in children 8 years of age and older and on proxy reported outcomes (parents or other caretakers) in younger children. Endpoints of clinical trials have traditionally measured changes in pain and bowel symptoms as well as measures of impact of these symptoms on the child's life such as quality of life and disability. However, there is no agreement on what constitutes an acceptable level of change in these symptoms,[33] nor there is agreement on which of the several different approaches to measuring change (anchor-based, distribution-based, or others) should be used.[34–36]

Recommendations for PRO and Proxy Reported Outcome for Abdominal Pain

Many different approaches have been suggested for PROs, including a global measure of change with treatment, a meaningful clinical important difference (MCID), and a percentage change in symptoms[21] As discussed previously, the EMA[18] and the FDA[17] recommended against the use of global outcome measures on the change in IBS symptoms such as adequate relief of symptoms with treatment (Table 2). In agreement with the regulatory agencies, this committee considered that the exclusive use of a global endpoints lacked specificity.

An alternative approach is to determine a MCID based on interviews with children, parents or physicians to determine a reduction in pain that corresponds

Table 2 Primary endpoints, entry and responder definition criteria for clinical trials on pediatric IBS*

Indication	Primary endpoints	Entry criteria	Responder definition
IBS-C	Abdominal pain intensity AND stool consistency	**Abdominal pain intensity** Weekly average of worst abdominal pain in past 24 h ≥3.0 on a 0–10 point scale or ≥30 mm in 100 mm Visual Analog Scale† **AND** **Stool consistency** Bowel movements during run-in period with average consistency <3 on the Bristol Stool Form Scale: Type 1 (very hard) or Type 2 (hard)	**Abdominal pain intensity** (Dual-criteria) ≥30% improvement in abdominal pain AND Improvement ≥Reliable Change Index (RCI) at the last week of trial compared with baseline **AND** **Stool consistency** Improvement in (≥1 Bristol Stool Form Scale to a higher number) average consistency at the last week of trial compared with baseline
IBS-D	Abdominal pain intensity AND stool consistency	**Abdominal pain intensity** Weekly average of worst abdominal pain in past 24 h ≥3.0 on a 0–10 point scale or ≥30 mm in 100 mm Visual Analog Scale† **AND** **Stool consistency** Bowel movements during run-in period with average consistency >5 on the Bristol Stool Form Scale: Type 6 (loose), 7 (very loose).	**Abdominal pain intensity** (Dual-criteria) ≥ 30% improvement in abdominal pain AND Improvement ≥Reliable Change Index (RCI) at the last week of trial compared with baseline **AND** **Stool consistency** Improvement in (≥1 Bristol Stool Form Scale to a lower number) average consistency at the last week of trial compared with baseline

*Abdominal pain endpoints alone to be used for trials on FAP-NOS. †Or similar cut off for moderate pain on different pain scale if used for PRO in the study.

with satisfactory pain control. Several studies have yielded MCIDs for pediatric pain measures[37]but most have been for acute pain and none have been conducted in pediatric IBS. Despite the strength of the reliance on child report of meaningful change, ratings of 'better' may vary with age[33]and this approach does not take into account that an absolute change may have a different meaning for children with different severity of symptoms. Hence, the committee recommends using a percentage change in pain instead.

The EMA and FDA have adopted the use of an improvement in abdominal pain equal or greater than 30% as primary endpoint for IBS in adult clinical trials.[17,18] It remains unclear if the endpoints recommended for adult studies are suitable for use in children. No trials have examined this. The subcommittee considered the EMA suggestion that a higher percentage of improvement of abdominal pain would be a preferred endpoint in children. No published evidence was found to substantiate this recommendation. A study comparing the use of at least 30% and at least 50% improvement in abdominal pain in children[38] showed that the use of the criterion: at least 50% improvement was more specific in detecting a positive response to a pain relief global question than the at least 30% criterion but the sensitivity of the at least 50% improvement in abdominal pain criterion was low (40%). Thus, the use of at least 50% improvement in abdominal pain as primary efficacy endpoint in clinical trials would result in a large proportion of children that considered their symptoms adequately relieved having negative results in clinical trials.

No PRO measure is perfectly reliable across administrations, and the test–retest reliability of a measure may vary as the interval between administrations increases.[34] Furthermore, due to developmental changes across childhood, children of different ages may vary considerably in their ability to report pain reliably over time. **In order to measure change reliably using PROS, the reliability of the measure needs to be considered.** A recent study has shown that less than half of subjects characterized as responders using the at least 30% criterion achieved a reliable change based on test–retest reliability and standard deviation of the pain measure.[33] Accounting for the test–retest reliability and standard deviation of pain measures can be done by calculating the Reliable Change Index (RCI; see appendix for formula) which is a measure of change in standardized units and it indicates the strength as well as the direction of the change. A change in pain that exceeds the RCI means the child is significantly improved. Thus, **the committee recommends that the endpoints for change should be a decrease of abdominal pain intensity of at least 30% from baseline and that this value should be at least equal to the RCI for that sample.** Examples of this process are provided in the appendix.

Applying these criteria require knowledge of the test–retest reliability of the pain measure to be used and standard deviation of the sample, before the start of the trial. However, the committee understands that there may be times when such estimates are not available and a standard estimate of the RCI is needed. Thus, **the subcommittee decided to provide an**

alternative endpoint to be used in cases that the calculation of the test–retest reliability of the pain measure and the standard deviation of the sample is not logistically possible. Based on the only study determining RCI among children ages 8–17 years with IBS, the RCI was 21.23 mm using a 0–100 mm VAS for abdominal pain[37] and exceeded the ≥30% change rule. In order to allow for variation among samples, the Rome Foundation Pediatric Subcommittee on Clinical Trials believes that a RCI of at least 25 mm should be used as abdominal pain endpoint. In order to assure enough pain severity to participate in a trial, the committee recommends a daily average minimum abdominal pain intensity of at least 30 mm on a 100 VAS or at least 3.0 out of 10 on a numeric rating scale (0–10).

Thus, for pain measures, the committee recommends the PRO to be based on a dual standard: change in pain meeting or exceeding both, 30% change in intensity from baseline and the RCI for that sample. An acceptable alternative to this approach, especially when no data is available to determine the RCI before the trial, is to use a cut-off of 25 mm change on a VAS.

Additional Recommendations Related to Measurement of Pain

1 Validated pain scales should be used for the assessment of chronic pain in children. These include the VAS and NRS or other scales with appropriate validation.[39–41]
2 As children vary widely in their ability to recall pain,[42] the committee recommends collecting daily 24-h recall of pain for at least 7 days. Pain intensity should be averaged over these 7 days. Daily diaries should be collected at least 7 days before the start of the trial and 7 days at the end of the trial while the child is still on medication. Minimum amount of time for trials is discussed elsewhere in this document.

Recommendations for PRO and Proxy Reported Outcome for Stool Consistency

Changes in stool consistency are the primary endpoints for both, IBS-D and IBS-C in children. The EMA[18] and FDA[17] proposed two co-primary endpoints for adults with IBS, the assessment of pain and stool characteristics. Stool assessment recommendations vary by IBS subtype. Both agencies proposed the assessment of stool consistency, measured by Bristol Stool Form Scale (BSFS) as outcome measure for IBS-D and stool frequency for IBS-C.[17,18] The committee considered that consistency and not frequency was a more relevant outcome in children with IBS-C and IBS-D. Thus, the committee recommends changes in stool consistency as primary endpoint for both, IBS-D and IBS-C in children. The trial may consider the use of frequency instead of consistency as primary endpoint if the predominant or exclusive action of the drug is to alter the frequency of bowel movements. **The committee recommends as entry criteria an average stool consistency lower than 3 in the BSFS during the run-in period for clinical trials on IBS-C and an average stool consistency greater than 5 in the BSFS during the run-in period for clinical trials on IBS-D.** Whenever possible and in every case in **children younger than 8 years of age, parents or caretakers should rate stool consistency** instead of the children. **Recording of stool characteristics should be done as close to the bowel movement as possible to avoid recall bias.**

Responder is defined as a patient who during the last week of the trial achieved an average change in stool consistency from baseline of at least one form in the BSFS (to a harder stool consistency in IBS-D and to a softer stool consistency in IBS-C). The committee recognizes that the validation of the BSFS in children is insufficient and the lack of data on MCID in stools in children. The use of the modified BSFS[43] was considered but the committee did not find enough evidence to recommend this tool or evidence that was superior to the original BSFS. The use of stool scales with a lower number of categories should be considered with caution as it may result in children requiring a greater change in stool characteristics to demonstrate benefit. This would result in studies that require a larger sample size to demonstrate a significant difference what may constitute an important limitation in pediatric clinical trials that frequently struggle to enroll a large number of children.

Recommendations for Secondary Measures

Although pain and stool consistency are the primary measures for assessing treatment outcomes, the subcommittee believes that the primary measure should ideally be complemented by secondary measures. **The most important secondary measure for clinical trials in IBS is disability.** A large part of the treatment of IBS is to reduce disability in children. Pediatric studies conducted on children with FADPs have shown that pain improvement does not always correlate with improvements of disability.[19] Children are frequently encouraged to attend school and participate in age appropriate activities no matter the level of pain. Therefore, **it is highly recommended to include a validated measure of disability in children.**

Other secondary measures of interest include pain frequency, equal or greater than 50% improvement in pain intensity, bowel movement frequency, no longer meeting Rome criteria for the condition being studied, quality of life and sleep. In addition, it is highly recommended to include in each trial parental report of primary and secondary outcome measures. Stool frequency and straining with bowel movements may be considered as secondary endpoints in children with IBS-C and IBS-D. Some pharmacological interventions may require the assessment of specific outcomes or mechanistic factors depending on the characteristics of the drug.

Recommendations for Data Analysis

Upon completion of the trial, the analysis should assess the proportion of patients in each treatment arm who fulfill a pre-established treatment responder definition that represents a clinically meaningful change to the patient (Table 3).

It is recommended that the analysis be conducted using an intention-to-treat principle, in which data from all patients enrolled are analyzed based on initial treatment assignment regardless of their completion of the trial or compliance with the protocol. The use of per-protocol analysis could be valuable as secondary analysis.

Interim analysis is not recommended. Interim analysis may jeopardize the integrity of the clinical trial and result in reporting of inaccurate observations. Interim analysis is justified when it is believed that participation in the trial may expose participants at risk.

Sample size calculation is required and assumptions for its calculation should be specified. Power calculations should be based on differences in proportions. The calculation of the sample size should be clinically relevant (powered to detect the MCID) and based on the expected behavior of the primary endpoints (expected difference in proportions between groups). Information on expected minimum effect size in primary outcomes between groups, type I error level, statistical power, and standard deviation of the difference if continuous outcomes will be considered should be provided. Lack of sample size calculation or lack of information on how the sample size is calculated is a common problem in pediatric RCTs in IBS.[1] An insufficient sample size may explain the negative results of some of the studies. At the time of sample size calculation, it should be considered that a high placebo effect may be present. Placebo effect in children across RCTs has been variable with one trial

Table 3 Summary of recommendations

General recommendations
- Primary endpoints should be based on patient reported outcomes (PROs) when possible.
- Entry criteria should be based on the Rome IV criteria.
- The use of daily diaries is recommended.
- Results should be evaluated using intention-to-treat principle.
- Interim analysis should be avoided.
- Selection of subjects should reflect the population that is affected.
- Demographic information on patients entered and excluded and reasons for exclusion should be documented.
- Demographic and clinical characteristics of the subjects in the medication and placebo group should be documented. Laboratory, imaging and endoscopic testing should be specified prior to the initiation of the trial.
- All adverse events should be documented and reported and be evaluated by a DSMB.
- Stopping rules have to be pre-established and documented in the study protocol.
- Treatment allocation and randomization should be specified and documented *a priori.*
- Trials should be registered in a public location.
- The results of the study should be published even if the results of the trial are negative or inconclusive.
- Sources of funding and conflicts of interest of each investigator should be disclosed.
- Participants should receive education, information and reassurance as standard care for IBS.
- Recording of stool characteristics should be done as close to the bowel movement as possible.
- Dropouts timing and reasons should be documented.
- Sample size calculation should be done and assumptions should be specified.
- For reporting of results the CONSORT guidelines should be followed.

Study design
- Randomized, double-blind (or triple-blind), placebo-controlled, parallel-group, clinical trial.
- Run-in period of at least 1 week.
- Study duration of at least 4 weeks.
- Two primary endpoints: abdominal pain intensity and changes in stool consistency (IBS-D and IBS-C) to be assessed as average value at the last week of the trial.

Patients with constipation predominant IBS (IBS-C) and diarrhea predominant IBS (IBS-D) should be studied in separate clinical trials. Similar recommendations apply to RCTs in children with a diagnosis of functional abdominal pain-not otherwise specified' (NOS) (FAP-NOS) with the exception of changes in stool characteristics.

showing a nocebo effect,[20] while other studies had a beneficial placebo ranging from 36% to 53%.[1] The multicenter trial by Saps *et al.* reported a placebo effect of 53% but a placebo effect as high as 75% was found if any improvement in the non-intervention arm would have been considered as a positive effect. RCTs for IBS in children had an attrition rate up to 19.4%.[44] Adjustments for dropout rate and loss to follow-up should be done. The procedures used for adjustment should be noted. Dropouts timing and when possible reasons should be documented.

CONSORT GUIDELINES

Studies should provide a detailed flow diagram and follow the CONSORT guidelines (http://www.consort-statement.org/).

COMMENTS

The current document is the culmination of the work of the Rome Foundation and members of the Pediatric Committee of the European Medicines Agency who aimed to bring standardization to the field and suggest best practices for pharmacological trials in children and adolescents.

Despite the recent emphasis on PROs, there is surprisingly little evidence in the pediatric literature to guide the design of clinical trials and the definition of clinically relevant and reliable outcome measures in pediatric IBS. There is considerable variation in entry criteria, length of duration of trial, and outcome measures in current pediatric trials.[1] Design and outcome measures for each trial either follow recommendations for adults with IBS or borrow heavily from acute pain trials. Neither approach is optimal as decisions for adults may not generalize well to children and pediatric acute pain measures have not been validated for IBS.

In a pediatric population one should be particularly concerned about reliability of measures in younger children in whom cognitive abilities to recall and report symptoms are still developing.[25] In addition, children may lack reading skills needed to complete questionnaires. Studies have shown good validity and reliability of several measures of acute pain, including non-verbal scales.[40,45,46] These scales have widely been used in the pediatric chronic pain literature. However, we do not know the reliability of these scales in chronic pain patients. For IBS patients, pain waxes and[47] and therefore needs to be assessed over several days to weeks, which raises issues of optimal timing for recall, duration of data collection to ensure representative data and what constitutes a meaningful difference in pain over time. Unfortunately, the subcommittee found no data on the validity and reliability of pain measures over prolonged periods of time and on what may constitute a meaningful difference in reduction of pain for pediatric IBS patients or chronic pediatric pain in general. We have even less data on stool endpoints for IBS. Similarly to the pain endpoint, there are few published data, and most scales (such as the BSFS) are not well validated in children[48] nor are meaningful differences defined. This gap in the literature hampered the subcommittee's ability to make evidence based recommendations on any of the current scales.

One study has tried to fill this void in the literature and determined meaningful differences of abdominal pain in a large study of pediatric IBS patients and found validation for defining a responder as at least 30% reduction in pain combined with exceeding the RCI of the pains[33]for a VAS this was defined as at least 25 mm reduction. This study is encouraging as it provides an empirical established estimate of a clinically meaningful difference. However, this study is in need of replication before we can recommend these cut-offs with any degree of certainty. Furthermore, this study used only one pain measure (a VAS of pain), and other measures may be of interest to researchers depending on the study population. For example, researchers may need to include non-verbal measure of pain in younger children, and estimates of meaningful clinical differences in chronic pain are currently not available for these measures. Based on the lack of evidence in pediatric pain measures, the subcommittee highly recommends for researchers embarking on trial design to collect additional data on reliability (RCI) of pain measures in children and adolescents with IBS.

In light of the lack of evidence on reliability of pain measures in children and adolescents with IBS the subcommittee recommends a two-pronged approach. The subcommittee recommends using the >30% change plus exceeding RCI rule. In order to do so, investigators need to collect additional data on reliability of their pain measures before embarking on trials. This not only ensures that trial data is reliable and meaningful, but also that more data will be collected on pediatric pain measures which will inform future trial design. If collection of reliability data is not feasible, the subcommittee recommends investigators use cut-offs determined in a previous trial of IBS using the VAS (≥25 mm change represents a responder).

Our recommendations on stool endpoints differ from EMA and FDA guidelines that recommend stool consistency in IBS-D and stool frequency in IBS-C as endpoints. The subcommittee considered that

consistency is a more meaningful outcome for children and that stool consistency was more clearly associated with the Rome definition of IBS-C and IBS-D that requires having hard stools or loose stools in more than 25% of days respectively. In addition, the subcommittee has polled authors of studies on pediatric IBS-C to obtain information on the number of daily bowel movements in children with this diagnosis. Data from two studies have shown that the mean number of bowel movements was variable among children with IBS-C with a wide spectrum that ranged from one to seven BMs a week.[48,49] These results are in agreement with a published study on IBS-subtypes in children that showed that the majority of children with IBS-C had >3 bowel movements weekly with 48% of children having one or more bowel movements daily.[50] These studies demonstrate that in children with IBS-C the frequency of bowel movements is highly variable and there is an overlap between the number of bowel movements in children with IBS-C and healthy children. Moreover, the use of number of bowel movements as endpoint in children that may be attending school during the trial and could withhold their stools either because they are not allowed to leave the classroom or to avoid the embarrassment of being noticed by their peers leaving the classroom to go to the bathroom could affect the number of bowel movements and provide inaccurate information. Children who have multiple bowel movements s a day may also not be able to accurately recall the number of bowel movements at the end of the day.

In addition to the primary PRO pain and stool, the subcommittee also considered important to measure disability. Reductions in disability (e.g., school avoidance) are important outcomes in IBS trials and may be independent of reductions in symptoms. Other secondary measures to consider were discussed. The subcommittee also included recommendations for trial design, largely based on best practices adjusted to the needs and ability of children. These include recommendations for study inclusion/exclusion criteria, measurement periods, child *vs* parental reports of PRO, trial duration, randomization, blinding etc.

FUTURE RECOMMENDATIONS

It is obvious that there are large gaps in knowledge in this field. Clearly, we are in need of studies to guide future recommendations. One of the most immediate pressing issues is to examine validity and stability over longer periods of time for the most common pain and stool measures. These studies should use intervals similar to those in RCTs. This information is needed in order to be able to assess the expected fluctuations in IBS symptoms that occur naturally and to estimate the strength of treatment effects when taking those fluctuations into account. Furthermore, studies are needed to determine developmentally appropriate meaningful differences in these measures, parent-child concordance of symptoms and how to optimize daily diaries of symptoms (e.g., by electronic diary). Studies on the effect of comorbid symptoms and the effect of somatization should be conducted to better understand the influence of these factors on the outcomes of clinical trials and to characterize subsets of patients that may achieve a greater benefit from each intervention. The effect of placebo in children and the factors that may influence its effect are in need of further investigation. We call on pediatric investigators to make trial design and measurement a focus of their study.

FUNDING

No funding declared.

DISCLOSURES

Miguel Saps: Scientific consultant Forest, Quintiles, Ardelyx, QOL Medical, IMHealth Science, Nutricia. Miranda A.L. van Tilburg: Takeda (research support). John Lavigne: No disclosures. Miranda Adrian: Scientific consultant QOL Medical, Marc Benninga: Scientific consultant Shire, Sucampo, Astrazeneca, Norgine, Zeria, Danone, Friesland Campina, Novalac. Jan Taminiau: No disclosures. Carlo Di Lorenzo: Scientific consultant QOL Medical, IMHealth Science, Merck.

AUTHOR CONTRIBUTIONS

Miguel Saps designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper, and critically reviewed the manuscript. Miranda A. L. van Tilburg designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper, and critically reviewed the manuscript. John Lavigne designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper, and critically reviewed the manuscript. Adrian Miranda designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper, and critically reviewed the manuscript. Marc Benninga designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper, and critically reviewed the manuscript. Jan Taminiau critically reviewed the literature and the manuscript. Carlo Di Lorenzo designed the study, contributed to the analysis of the published data, contributed to the development of recommended guidelines, wrote the paper and critically reviewed the manuscript.

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APPENDIX

CALCULATING THE PRO BASED UPON THE DUAL CRITERIA OF EXCEEDING THE 30% IMPROVEMENT AND RCI VALUE

Procedures for calculating the RCI are described by Jacobsen and Truax (1992). Table 1 illustrates RCIs for various combination of test–retest correlations and standard deviations of the pre-treatment sample that will apply to most clinical trials. To illustrate, in a sample in which the test–retest reliability is .8 and the SD for the pretreatment sample is 20, the RCI would be 24.79. As scales vary widely in their scoring, the standard deviation may vary, as illustrated for the VAS (figure 1a) and Faces Pain Scale (A1 [B]).

Table 2 illustrates the process of combining the RCI and the 30% FDA criteria to achieve the dual standard PRO recommended by the subcommittee. As illustrated, the magnitude of the final value reported by the child to meet the 30% change standard varies with the pretreatment (baseline) score. In Table A2, the RCI was based on a sample in which the test reliability is 0.80 and the pre-treatment SD is 20. In that instance, as Table A2 shows, the dual-criteria PRO for the child whose initial VAS score was 100 would be 30 (because the 30% change score is greater than the RCI). For a child with an initial VAS score of 50, the MCID would be 25 (because the RCI is greater than the 30% change criteria). Thus, a child with an initial VAS of 50 would need to change by ≥25 to be classified as a responder. Again, a similar process can be used for other measures, such as the revised Faces scale (See Table A3).

Table A1 (A) RCI of the Visual Analog Scale. (B) RCI for the Faces Pain Scale

	Test–retest correlation						
SD value	0.7	0.75	0.77	0.8	0.85	0.9	0.95
(A)							
10	15.18	13.85	13.29	12.4	10.73	8.76	6.2
15	22.77	20.79	19.94	18.59	16.1	13.14	9.29
20	30.64	27.71	26.59	24.79	21.47	17.53	12.4
30	45.54	41.58	39.88	37.18	32.2	26.3	18.59
(B)							
1	1.51	1.38	1.23	1.24	1.07	0.88	0.62
1.5	2.28	2.08	1.99	1.86	1.61	1.31	0.93
2	3.03	2.77	2.69	2.4	2.15	1.75	1.24

Table A2 Dual criteria PRO for VAS

VAS score (baseline)	FDA 30%	30% reduction value	RCI*	PRO based on dual criteria
100	0.3	30	25	30
90	0.3	27	25	27
80	0.3	24	25	25
70	0.3	21	25	25
60	0.3	18	25	25
50	0.3	15	25	25
40	0.3	12	25	25
30	0.3	9	25	25
20	0.3	6	25	25
10	0.3	3	25	25

*Estimated for a trial in which the test–retest reliability of the VAS is .80 and the sample SD is 20. The 24.79 RCI value (Table 1) was rounded to 25.

Table A3 Dual criteria PRO for Faces Pain Scale

FACES/NRS (initial)	FDA 30%	30% reduction value	RCI*	MCID based on dual criteria	Rounded MCID
10	0.3	3	1.86	3	3
9	0.3	2.7	1.86	2.7	3
8	0.3	2.4	1.86	2.4	3
7	0.3	2.1	1.86	2.4	3
6	0.3	1.8	1.86	1.86	2
5	0.3	1.5	1.86	1.86	2
4	0.3	1.2	1.86	1.86	2
3	0.3	0.9	1.86	1.86	2
2	0.3	0.6	1.86	1.86	2
1	0.3	0.3	1.86	NA	NA

*Estimated for a trial in which the test–retest reliability of the scale is .80 and the sample SD is 1.5. in the last column, the 1.86 RCI value was rounded to 2.