Pediatric functional abdominal pain disorders

From diagnosis to management - a clinical approach

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CHAPTER 8

A Core Outcome Set for Clinical Trials in Pediatric Functional Abdominal Pain Disorders

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ABSTRACT

Objective: To ensure consistency and reduce outcome measure reporting heterogeneity in clinical trials on pediatric functional abdominal pain disorders (FAPDs), a core outcome set (COS) was developed for pediatric FAPD trials.

Study design: A mixed-method 2-round Delphi technique was used and key stakeholders, including healthcare professionals (HCPs), patients with FAPD, and their parents were invited to participate. In the first round, key stakeholders identified outcomes of importance through an open-ended questionnaire. Outcomes mentioned by ≥10% of the participants were included in a shortlist. In the second round, this shortlist was rated and prioritized. During a consensus meeting with an expert panel, the final COS was defined.

Results: The first round was completed by 152 of 210 (72%) HCPs, 103 (100%) parents, and 50 of 54 (93%) patients. A total of 104 from 167 (62%) HCPs, 102 (100%) parents, and 53 (100%) patients completed round 2. Pain intensity, pain frequency, quality of life, school attendance, anxiety/depression, adequate relief, defecation pattern (disease specific, irritable bowel syndrome), and adverse events were included in the final COS for FAPDs.

Conclusion: A set of 8 core outcomes has been identified that should minimally be measured in pediatric FAPD trials. Implementation of the use of this COS will increase comparison between studies and, therefore, improve management of children with FAPDs.

BACKGROUND

Chronic abdominal pain in childhood is a common problem with a worldwide prevalence of 13.5%.[1] In the majority of children, symptoms cannot be attributed to a medical condition after appropriate evaluation.[2] These children can be diagnosed with 1 of the 4 functional abdominal pain disorders (FAPDs) according to the Rome IV criteria: functional dyspepsia, irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain not otherwise specified.[3] The impact of FAPDs on daily life is substantial, as pediatric patients report a lower quality of life, more school absenteeism, and more depressive and anxiety disorders compared with healthy controls.[4-6] In addition, healthcare costs are substantial.[7] Underlying pathophysiological mechanisms of FAPDs are complex. FAPDs are considered multifactorial disorders, explained by a complex interplay between genetic, physiological, and psychological factors that together form the biopsychosocial model.[8] Treatment consists of an integrated approach, involving education, reassurance, dietary advice, pharmacologic, and nonpharmacologic management, such as behavioral and psychological interventions.[9] However, clinical management is hampered as results of treatments from different pediatric trials concerning FAPDs, are hard to compare due to a lack of uniform definitions and homogeneous outcome measures.[10-14] A systematic review on outcome measures in pediatric FAPDs including 64 randomized controlled trials (RCTs) demonstrated that 211 different predefined outcome measures grouped into 23 different outcome domains were used to investigate the effectiveness of FAPD interventions.[10]

To improve comparison between studies and enhance clinical management, standardization of definitions, measurement and reporting of outcomes should be the goal. This can be accomplished by the development and implementation of a core outcome set (COS); a standardized consensus-driven set of outcomes that should be measured and reported at minimum in all RCTs for a certain health condition.[15,16] These reported outcomes are not only relevant to healthcare professionals (HCPs), but also to patients and their families, because patient-reported outcomes are increasingly being recognized in clinical practice and research.[17] This is in line with the recommendations of the Outcome Measures in Rheumatology Initiative (OMERACT) and Core Outcome Measures in Effectiveness Trials (COMET) initiatives, which successfully developed COSs in other healthcare areas.[15,18]

The aim of the present study was to develop a COS for therapeutic trials in pediatric FAPDs according to the OMERACT and COMET recommendations using a 2-round Delphi process, ensuring active involvement of key stakeholders (ie, HCPs, parents and patients) throughout the development of this COS.

METHODS

The development of this COS was performed through adherence to the OMERACT Filter 2.0 and COMET recommendations[15,18] using a mixed-method approach, which integrates qualitative with quantitative research. This was exercised through the use of a 2-round Delphi survey; this technique is often used in COS development.[18]

The development process of our COS consisted of 4 phases: (1) Identifying existing knowledge through a systematic review of present literature; (2) Elicit outcome measures of importance through a qualitative, open-ended questionnaire filled out by key stakeholders (Delphi round 1); (3) Ranking of outcomes and creation of shortlists (Delphi round 2); and (4) Finalizing of the COS during a consensus meeting.

Key stakeholders included HCPs, parents of patients with a FAPD, and patients themselves (age 4-18 years). For the reporting of this COS, we followed the COS standards for reporting statement.[19] This study was exempted from review by the Medical Ethical Committee of the Amsterdam University Medical Centers, location Amsterdam Medical Center, The Netherlands.

Phase 1 – Systematic Review

To set the scope of this COS through identification of existing knowledge, a systematic review was performed to assess which definitions of FAPDs and outcomes measures were reported in therapeutic RCTs in pediatric FAPDs. Detailed methods are described elsewhere.[10]

Phase 2 – Identification of Important Outcome Measures of Treatment

HCPs

During the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2018 annual meeting in Geneva, Switzerland, and the

Digestive Disease Week 2018 in Washington DC, US, HCPs were invited to participate in our study by filling out an open-ended questionnaire as first round of the Delphi technique.[18] HCPs in Australia were invited through personal networks. All HCPs who were experienced in the care of children with FAPDs were included. There were no restrictions with regard to age, level of expertise, or setting of care. The English-written survey was distributed by paper, and participants were asked to list up to 5 important outcomes of treatment that guide clinical decision making in children with FAPDs, separately for the outpatient and inpatient setting (**Appendix 1**). Furthermore, data on profession and country of practice were collected. FAPDs were defined according to the Rome IV criteria and included functional dyspepsia, IBS, abdominal migraine, and functional abdominal pain not otherwise specified.[3] Data were processed anonymously. Similar to previous COS development studies, our aim was to include ≥150 HCPs.

Parents and Patients

In 5 different countries (Belgium, Italy, The Netherlands, Australia, and Sri Lanka), parents of children with an FAPD and patients themselves (age 4-18 years), were invited to participate in the study. Parents and patients were unrelated. We aimed to include 100 parents (20 per country) and 50 patients (10 per country). Again, these numbers were based on previous studies.[20–22] Diagnosis of an FAPD was made by the treating physician of the child, based on the Rome IV criteria and clinical interpretation. During consultation at the outpatient clinic, the treating physician invited the participants to fill out an anonymous paper survey. Parents had to list up to 5 results of treatment or scenarios that made them feel comfortable/uncomfortable and gave them the feeling their child was being treated adequately/inadequately.[11] The same survey with adapted language for children was presented to 5 patients as a pilot. Their comments were processed to refine the survey and the questionnaire was then distributed to the participating countries. Surveys (**Appendix 2** and **Appendix 3**) were developed in English and presented to participants in their native language. In the non-English speaking countries, the translated surveys were also presented to 5 parents and 5 patients as a pilot. Comments were processed and questionnaires were distributed accordingly. The experienced researchers that questioned the parents and patients translated the answers back into English.

Analyses and Creation of Shortlists

All outcomes provided by the different stakeholders were judged independently by 3 investigators. Disagreements were discussed with a fourth investigator; this occurred in less than 10% of the outcomes. Different definitions for the same outcome were grouped where possible, for example "no pain," "no episodes of pain," and "no abdominal pain" were all grouped under "no abdominal pain." Another example was the grouping of "abdominal pain better," "pain improves," and "less pain" into "abdominal pain reduction." These grouped outcomes were categorized into different outcome domains and core areas according to the OMERACT framework[15] and the published systematic review.[10]

Responses of the HCPs were analyzed separately for the in- and outpatient setting. Responses of parents on comfortable and uncomfortable outcome measures were combined in case of similarity. For example, the comfortable outcome measure "no abdominal pain" and the uncomfortable outcome measure "abdominal pain" were combined into 1 outcome measure "abdominal pain," which could be forwarded to round 2. Another example was the grouping of the comfortable outcome measure "school attendance" and uncomfortable outcome measure "school absence" into "school attendance." In this way, the domain of the outcome measures was retained, but the distinction between "comfortable" and "uncomfortable" outcomes was removed to avoid indistinctness of having 2 outcome measures on the shortlist of round 2 with the same meaning. The outcome measure (ie, comfortable or uncomfortable) that was reported most often was used to define the combined outcome measure. The same method was applied to patient responses. Grouped outcomes that were mentioned by ≥10% of the key stakeholders were selected for 4 different shortlists: 2 for the HCPs for the in- and outpatient setting and 2 based on the answers of the parents and patients, respectively, regardless of setting.

Phase 3 – Prioritization of Outcomes

HCPs

HCPs who consented in the first Delphi round to participate in the second round, were contacted by email. Furthermore, members of the ESPGHAN and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and Australian HCPs were invited as well. They were asked to rate the importance of the outcomes on

the shortlists from round one using a 9-point Likert scale (1–3 = limited importance, 7–9 = critically important). An outcome was included in the preliminary COS, defined as "consensus in," if ≥70% of the HCPs scored it as "critically important" (7–9) and ≤15% of the HCPs scored it as "limited importance" (1–3).[16]

Parents and Patients

In the same 5 countries as listed above, a new group of parents (n = 20 per country) and patients (n = 10 per country) were invited to participate in the second Delphi round. Parents and patients were unrelated. Parents were asked to rate the outcomes on the parental shortlist on a scale of 0–4 (0 = does not make me feel comfortable, 4 = makes me feel very comfortable). Patients were asked to do the same for their shortlist, using a 0–4 scale with adapted language (0 = makes me feel worried/upset, 4 = makes me feel very happy) and a modified Wong Baker Faces Pain scale (5 faces), with every face representing one of the 5 points on the Likert scale.[23–25] Furthermore, parents and patients were asked to prioritize these outcomes by listing up the 5 outcomes that made them feel the most comfortable. Next, the 5 outcomes with the highest rank were selected for the preliminary COS for the patients and parents, respectively. The questionnaire for patients in this round was piloted as well.

Phase 4 – Finalization of COS

During the 52nd ESPGHAN 2019 annual meeting in Glasgow, United Kingdom, a face-to-face consensus meeting was held to finalize the COS. An expert panel of pediatric gastroenterologists discussed the results of the Delphi survey and agreed on their final list of outcomes that had to be included in the COS. Only in case of a unanimous decision of the expert panel, consensus was reached.

RESULTS

The systematic review found a large heterogeneity and inconsistency in defining FAPDs and outcome measures in therapeutic trials in pediatric FAPDs.[10] A total of 152 from 210 (72%) HCPs completed the first questionnaire. Characteristics are displayed in **Supplemental Table 1.**

HCPs reported a total of 81 outcome measures for the outpatient setting and 82 for the inpatient setting. Eight outcomes were excluded for the outpatient setting,

and 10 outcomes were excluded for the inpatient setting because of unreadability or irrelevancy to the scope of this COS (**Supplemental Table 2**). For the outpatient setting, 13 outcome measures were reported by ≥10% of the HCPs and, thus, forwarded to the shortlist for Delphi round 2. The shortlist of the inpatient setting included 11 outcome measures.

Overall 103 (100%) parents of patients with FAPD completed the first Delphi round. In 56 (55%) cases, the questionnaire was completed by the mother, in 20 (19%) cases by both parents, in 5 (5%) cases by the father, and in 22 (21%) cases it was unclear. **Supplemental Table 3** demonstrates the 49 different outcomes reported by the parents. Three outcomes were excluded due to unreadability or irrelevancy to the scope of this COS (**Supplemental Table 3**). Fifteen outcome measures were forwarded to the shortlist of Delphi round 2 as they were reported by ≥10% of the parents.

The first Delphi round for patients was completed by a total of 50 (93%) children. Of them, 27 (54%) completed the questionnaire with help from (one of their) parent(s) and 23 (46%) completed the questionnaire on their own. Median age of the patients was 11 years (IQR 8–13). **Supplemental Table 4** lists the 26 outcome measures reported by the patients. Of them, 14 were mentioned by ≥10% of the patients and were, therefore, included in the shortlist for Delphi round 2. No outcomes were excluded.

A total of 167 HCPs were approached by email by the researchers for round 2 of the Delphi process. Of them, 104 (62%) rated and prioritized the outpatient and inpatient shortlists. **Supplemental Table 1** displays their characteristics.

Results of the prioritization of outcomes by HCPs for the outpatient and inpatient setting are summarized in **Table 1**. A total of 8 outcomes for the outpatient setting and 4 outcomes for inpatient setting met criteria for the "consensus in." Outcomes of the outpatient and inpatient setting were then combined, and this resulted in 9 unique outcomes that were forwarded to the preliminary COS (**Table 1**).

Table 1. Shortlist of outcome measures rated and prioritized by HCPs (n=104) for the outpatient and inpatient setting

Ranks	Outcome measure	Average rating (1 – 9)	Percentage (%) (1 – 3)	Percentage % (7 – 9)
Outpatient setting				
1.	**Quality of life**	**7.77**	**0.0**	**86.6**
2.	**Pain reduction**	**7.49**	**2.0**	**78.9**
3.	**Pain intensity/severity**	**7.44**	**1.0**	**77.9**
4.	**Daily/social functioning**	**7.32**	**0.0**	**79.7**
5.	**School attendance**	**7.30**	**3.8**	**77.9**
6.	**Pain frequency**	**7.21**	**0.0**	**74.1**
7.	**Growth/failure to thrive**	**7.27**	**7.7**	**75.9**
8.	**Anxiety/depression**	**6.98**	**4.8**	**74.0**
9.	Doctor/hospital/emergency visits	6.35	1.9	51.9
10.	Bowel movements	5.74	13.5	38.5
11.	Use of nonpharmacologic treatment	5.63	12.5	31.8
12.	Use of pharmacologic treatment	5.57	8.7	28.9
Inpatient setting				
1.	**Pain intensity/severity**	**7.61**	**1.9**	**81.7**
2.	**Adequate reassurance**	**7.31**	**3.8**	**74.1**
3.	**Pain frequency**	**7.25**	**1.9**	**77.0**
4.	**Quality of life**	**7.20**	**1.9**	**73.0**
5.	Growth/failure to thrive	7.07	8.7	68.3
6.	Daily/social functioning	6.87	2.9	58.6
7.	Length of hospitalization	6.79	4.8	63.5
8.	School attendance	6.58	12.5	59.9
9.	Use of pharmacologic treatment	6.23	3.9	49.0
10.	Frequency of additional investigations	6.19	8.7	45.2
11.	Use of nonpharmacologic treatment	5.63	14.4	33.6

Outcomes that were rated by >70% of the respondents as 7–9, and by <15% as 1–3 were included in the preliminary core outcome set and are highlighted in bold.

Round 2 of the Delphi process was completed by 102 (100%) parents of patients with a FAPD. Five outcomes (ie, no abdominal pain, normal daily functioning, normal stools, parental reassurance, and abdominal pain reduction) were forwarded to the preliminary COS (**Table 2**).

Fifty-three (100%) patients with a FAPD completed Delphi round 2. Their median age was 12 years (IQR 9-15). **Table 2** demonstrates the rated and prioritized outcomes of the shortlist from Delphi round 1.

Table 2. Shortlist of outcome measures rated and prioritized by parents (n=102) and patients (n=53)

Ranks	Outcome measure	Average rating (0 -4)	Percentage (%)*
Parents			
1.	**No abdominal pain**	**3.68**	**87**
2.	**Normal daily functioning**	**3.39**	**77**
3.	**Normal stools**	**3.13**	**53**
4.	**Abdominal pain reduction**	**3.11**	**63**
5.	**Parental reassurance**	**3.08**	**43**
6.	Psychological improvement	3.02	40
7.	School absence	1.52	34
8.	No adequate intake/appetite	1.51	18
9.	Nausea	1.50	17
10.	Tiredness of the child	1.47	13
11.	Constipation	1.34	19
12.	Side effects of treatment	1.05	3
13.	Vomiting	0.90	14
14.	No improvement of symptoms	0.90	12
15.	Diarrhea	0.79	7
Patients			
1.	**No abdominal pain**	**3.81**	**91**
2.	**Good daily functioning**	**3.50**	**78**
3.	**Good appetite**	**3.16**	**52**
4.	**Less severe abdominal pain**	**3.10**	**66**
5.	**Less often abdominal pain**	**3.10**	**57**
6.	Mood improvement	3.02	34
7.	Less frequent stools	2.21	17
8.	Changing stools (hard/soft)	1.95	9
9.	Use of medication	1.81	5
10	Diarrhea	1.38	24
11.	Nausea	1.28	17
12.	Constipation	1.21	19
13.	Missing school	1.10	22
14.	Headache	1.06	5

Outcomes that were included in the preliminary COS are highlighted in bold.
*Percentage of parents and patients that prioritized the outcome measure in their top 5 most comfortable outcomes.

Preliminary COS

The 9 outcome measures of the preliminary COS of HCPs were combined with the 10 outcome measures of the preliminary COSs of parents and patients (**Figure 1, step 1**). After careful consideration by the team, these 19 outcome measures were reduced to 11 outcome measures for the draft COS, as some of these outcomes could be grouped together (**Figure 1, step 2**). Furthermore, the outcome measure "adverse events" was added to the draft COS, because it is recommended by OMERACT that treatment effect in therapeutic trials should not only be measured through benefit, but also through potential harm.[15]

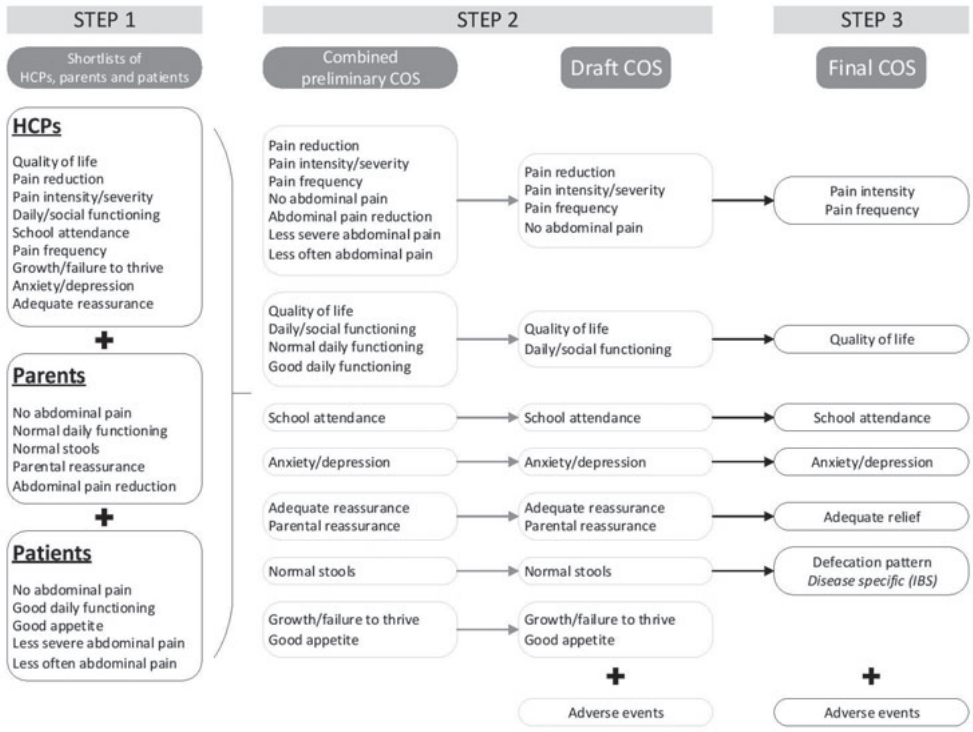

Figure 1. Preliminary, draft, and final COS for pediatric FAPDs. In step 1, the shortlists of HCPs, parents, and patients were combined. In step 2, the following outcomes of the combined preliminary COS were grouped together for the draft COS based on expert opinion of the research team: "abdominal pain reduction" was grouped under "pain reduction"; "less severe abdominal pain" was grouped under "pain intensity/severity"; "less often abdominal pain" was grouped under "pain frequency"; "normal daily functioning" and "good daily functioning" were grouped under "daily/social functioning". Furthermore, adverse events were added following the methodology. In step 3, the draft COS was discussed during the consensus meeting: "pain reduction" and "no abdominal pain" were grouped under "pain intensity" and "pain frequency"; "daily/social functioning" was grouped under "quality of life"; and "adequate reassurance" and "parental reassurance" were grouped under "adequate relief". The final COS consists of 8 core outcome measures.

Consensus Meeting

Six HCPs, originating from Europe (n = 4), Asia (n = 1), and Australia (n = 1), participated in the consensus meeting. During this meeting, the draft COS was presented. Following discussion, the outcome measures "good appetite" and "growth/failure to thrive" were unanimously excluded from the draft COS because these outcomes were nonspecific for FAPDs and they could not with certainty be attributed to a treatment effect of FAPDs. Finally, 8 core outcomes were included in the COS: pain intensity, pain frequency, quality of life, school attendance, anxiety/depression, adequate relief, defecation pattern (disease-specific for IBS), and adverse events (**Figure 1, step 3**).

DISCUSSION

In this study, a COS was developed for therapeutic trials in pediatric FAPDs, consisting of 8 core outcomes. These outcomes were agreed upon by an international panel of HCPs, parents, and patients using a 2-round Delphi technique.

Abdominal pain was rated as most important outcome by parents of patients with FAPDs and patient themselves, and HCPs ranked abdominal pain as second most important outcome. The comparability of this result underlines the importance of this clinical feature for therapeutic trials in pediatric FAPDs and has been supported by a guideline for the design of pediatric pharmacologic trials.[26] However, this guideline discriminates between abdominal pain intensity and frequency, as these are 2 different aspects of abdominal pain.[26] In line with this guideline and in line with the findings from our previous performed systematic review on outcome measures in pediatric FAPDs,[10] it was decided during the consensus meeting that a distinction should be made between abdominal pain intensity and frequency in the final COS.

HCPs rated quality of life as most important outcome measure, whereas this outcome was not listed on the shortlist of parents and patients after Delphi round 1. This is in line with other COS development studies.[20,22] One would expect this patient-reported outcome to be recognized by parents and patients as well. It might be hypothesized that HCPs are more familiar with the term quality of life, whereas parents and patients might mean the same, but paraphrase it in a different way, such as good daily functioning. This was one of the reasons the expert panel decided to combine quality of life and daily/social functioning into quality of life

for the final COS. The fact that quality of life is one of the core outcomes in our COS is important, as this outcome reflects the patient's perspective on healthcare which is becoming increasingly important in daily clinical practice.[15,17,18]

Another difference in rated and prioritized outcome measures between the different stakeholders was found for the outcome measure school attendance, which was rated as important by HCPs in both Delphi rounds. However, parents and patients did not rank it in the top 5 most important outcome measures after Delphi round 2. Although it has been demonstrated that children with FAPDs show significantly more school absenteeism than healthy controls,[5] our study demonstrates that parents of children with FAPDs and patients themselves considered abdominal pain and daily functioning more important than school attendance. It might be suggested that HCPs, in specific pediatric gastroenterologists, value school attendance and, thus, social functioning, as important, because this will distract the child from their complaints, which has been shown to decrease their complaints.[27] Parents of patients with FAPD tend to be overprotective[28] and pay attention to their child's complaints, thereby reinforcing somatic symptoms.[27] They have to be reassured by their treating physician that distraction from their child's complaints can help their children cope with symptoms.[27]

One of the strengths of our study is the response rate of >60% in both Delphi rounds. This is comparable with other COS development studies.[11,20–22] Furthermore, HCPs from more than 30 different countries, divided over 5 continents, were included in our study. Developing countries, such as Sri Lanka, were also represented. In addition, parents of children with FAPDs and FAPD patients themselves were recruited in 5 different countries from distinct continents, including the developing country Sri Lanka as well. Therefore, global representation was substantial in our study, leading to international applicability of our results. This is in line with the COMET guideline, which supports global consensus.[18] Overall, no important differences in outcome measures between countries were found. Another strength of our study is that we included both parents of patients with FAPDs and patients with a FAPD themselves. Because the effect of a treatment for pediatric FAPDs affects the children themselves the most, it is important to take their opinion into account when deciding what to measure as treatment effect. Although it might be suggested that parents may reflect the needs of their children as well, it has been demonstrated that differences exist between parent- and patient-report of child somatic symptoms.[29,30] Therefore, the inclusion of patients as participants in

developing COS will enhance the acceptability of therapeutic trials for patients and thereby increase their involvement in clinical decision making. Patient integration in COS development is recognized and encouraged by the COMET and OMERACT initiatives as well.[15,18] Finally, the Delphi technique used in our study provides a structured way to reach consensus through sequential rounds of questionnaires.[18] It is advantageous as it avoids the effect of dominant individuals due to its anonymity, and it can be used in large numbers with worldwide distribution.[18]

One of the limitations of our study is that we used qualitative questionnaires as part of our COS development process. Therefore, some results were prone to interpretation by the researchers. This may have led to confirmation bias, especially when researchers combined outcome measures that were comparable in their beliefs. In line with previous COS studies, it was decided to give no feedback of results between rounds to participants. However, this might have reduced the confirmation bias. Moreover, the original questionnaires were developed in English and translated to the native language of the parents and patients by the researchers who invited them to participate. Afterward, these researchers translated the given answers back into English. This may have led to misinterpretation of responses as well. Furthermore, the questionnaires for the 3 different stakeholder groups (HCPs, parents, and patients) differed with regard to the formulation of the questions, which was adapted for each target group. In addition, the HCPs rated the importance of the outcome measures in Delphi round 2 on a 9-point Likert scale, whereas parents and patients rated them based on a 5-point Likert scale. These discrepancies may partly explain differences in results between stakeholder groups. However, the 9-point Likert scale entails an advantage as well because it reduces the risk of confirmation bias that might be caused by researchers interpretations.[16]

Despite the fact that we included HCPs from 3 different care settings (primary, secondary and tertiary care), the majority (>66%) practiced in a tertiary care setting. This might be a limitation, as this may have limited the external validity of our COS to primary and secondary care settings. Although most clinical trials are conducted in the hospital setting,[10] the study should be replicated amongst primary care doctors. However, the inclusion of tertiary care HCPs might also be a strength, as they are highly experienced in treating pediatric FAPDs and this COS study was developed for therapeutic trials on pediatric FAPDs. Because the first steps in the treatment of children with FAPDs (ie, reassurance and then either

a pharmacologic or nonpharmacologic intervention) are comparable between primary, secondary, and tertiary care settings,[31] results of our study should be generalizable to primary care as well.

Because of the relatively small number of parents and patients included in our study, we were not able to perform subgroup analyses for the different FAPDs, which is a considerable limitation. It could be possible that some disease-specific outcome measures, such as early satiation or postprandial fullness for functional dyspepsia, were therefore missed and are not included in the final COS. However, of the 8 core outcome measures of the final COS all but 1 includes generic measures, which are relevant for all 4 FAPDs. During the consensus meeting, 1 exception has been made by the expert panel to include the IBS-specific outcome measure "defecation pattern." This outcome measure was rated as very important by parents, therefore, the expert panel decided to include this as a core outcome. Unfortunately, and because of logistical and financial reasons, parents and patients were not able to attend the consensus meeting. However, when comparing the current COS for FAPDs to other recently developed COSs in the pediatric gastrointestinal field,[20–22] it is noted that several outcome measures, such as "abdominal pain," "quality of life," "adequate relief," and "adverse events" overlap. Therefore, it might be suggested that HCPs and parents consider similar treatment results important, irrespective of the underlying condition of the pediatric patient. This may advocate for the use of a more general COS, with the option to expand it with disease-specific outcome measures.

One of the challenges of this COS lies in the next phase, in which it will be determined how selected outcome measures in the final COS will be defined and measured. Pooling of results of clinical trials is not only hampered by heterogeneity in outcome measures, but also by incomparable scores from different instruments. The previously performed systematic review on outcome measures in pediatric FAPDs demonstrated that great heterogeneity exists in the measurement tools used to assess primary and secondary outcomes in therapeutic pediatric FAPD trials.[10] For example, pain frequency and pain intensity, 2 of the 8 core outcomes of our final COS, were measured in 11 different ways.[10] Not only the measurement instrument, but also the specific metrics used to characterize each patient results varied widely. Specific metrics for pain frequency were for example "number of pain episodes per day," "mean number of pain episodes per week," "no pain episodes per week" etc. This illustrates the need for consensus on *how* to measure

the 8 core outcomes of our final COS. The validation of a pain diary might be suggested, as well as the use of the validated adequate relief question,[32] which is in line with the trial recommendations.[26] Specific attention should be given for the outcomes that were included in the draft COS but that were grouped into another outcome measure for the final COS, such as daily functioning or parental reassurance. For these outcome measures, recommendations for measurement instruments should be made separately, as these outcome measures will not be included in the final COS initially, but are part of the combined final core outcome.

The recommended COS is comparable with the findings of our systematic review in phase 1 of the COS development process.[10] The systematic review found that pain intensity and pain frequency were the most often reported primary outcome domains, whereas functioning and psychological health were the most often reported secondary outcome domains. Five of the 8 core outcomes of the final COS of this study are in accordance with these most reported outcome domains of the systematic review. This underlines the potential applicability of our final COS in trials and illustrates the importance of these outcomes for researchers.[10] However, with the development of this COS, parents and patients were involved and were allowed to reflect on the importance of outcome measures. It has been recognized by the COMET initiative that parent and patient contribution is crucial, as this increases the relevancy of the COS and enhances clinical decision making.[18]

In conclusion, the final COS for pediatric FAPD trials includes the following 8 core outcomes: pain intensity, pain frequency, quality of life, school attendance, anxiety/depression, adequate relief, defecation pattern (disease-specific for IBS), and adverse events. The use of this COS in clinical practice, observational studies, and RCTs will provide comparable results that will be of great importance to guide the treatment of children with FAPDs and which will hopefully lead to improved clinical management of these children.

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SUPPLEMENTARY FILES

Supplementary material of chapter 8 is available online

Appendix 1. Questionnaire HCPs

Appendix 2. Questionnaire Parents

Appendix 3. Questionnaire Patients

Supplemental Table 1. Characteristics of HCPs participating in Delphi round 1 and 2

Supplemental Table 2. Identification of outcome measures of importance by HCPs for the outpatient and inpatient setting (n = 152)

Supplemental Table 3. Identification of outcome measures of importance by parents (n = 103)

Supplemental Table 4. Identification of outcome measures of importance by patients (n = 50)