Pediatric functional abdominal pain disorders

From diagnosis to management - a clinical approach

Rexwinkel, R.

Publication date
2023

THESIS SUMMARY AND GENERAL DISCUSSION

Thesis summary

General discussion

Nederlandse samenvatting

THESIS SUMMARY

Functional abdominal pain disorders (FAPDs) are common in pediatrics and according to the Rome IV criteria they can be divided into four different subcategories: (1) functional dyspepsia (FD), (2) irritable bowel syndrome (IBS), (3) abdominal migraine (AM), and (4) functional abdominal pain – not otherwise specified (FAP-NOS).[1,2] These disorders are characterized by chronic abdominal pain (≥2 months), and in the case of IBS, alterations in stool pattern.[1,3] FAPDs in children are associated with decreased quality of life and school attendance, but the pathophysiology underlying FAPDs is not completely understood and diagnosis is generally symptom-based.[4-6] Due to the heterogeneity of therapeutic trials and the quality of evidence supporting these interventions, management of childhood FAPDs remains challenging.[7] This thesis describes novel insights regarding diagnostic and management strategies, shared decision making (SDM) and clinical outcome measures for research, with the aim to enhance patient care, improve quality of care, and allow better evidence-based decision making.

In **part I** of this thesis, we focus on improving pediatric FAPD **diagnosis**. We evaluated the use of pictograms to improve symptom evaluation and the clinical value of two screening workups. In **part II and III** of this thesis, we focus on different **management** strategies. Current available treatment options for pediatric patients with FAPDs include education, reassurance and lifestyle changes, non-pharmacological options, such as psychosocial interventions, and pharmacological options. However, management remains mostly symptom-based because no gold standard of treatment exists. To give an up-to-date overview on the efficacy and safety of most used interventions, we described the results of three systematic reviews on psychosocial, dietary and pharmacological interventions in children with FAPDs. **Part IV** of this thesis describes the implementation and feasibility of a **SDM**-intervention in children and the development of a '***core outcome set***' (COS), an agreed minimum set of outcomes that should be measured and reported in trials in a certain area.

PART I – Diagnostics

History taking and physical examination to identify possible alarm symptoms are the first steps in the clinical evaluation of children with FAPDs.[1] In clinical practice it might be challenging for children to adequately describe their symptoms.

This can hamper communication between the child, parent(s) and healthcare professional (HCP). The use of Patient Reported Outcome Measures (PROMs), by using pictograms, may overcome this barrier and can increase the comprehension of symptom description during consultations.[8–11] Hence, in **chapter 1**, we evaluated whether the use of pictograms improves symptom evaluation for children with FAPDs. 144 children (aged 8–18 years) from two academic centers (Amsterdam and Leuven) were included in this survey study. This study showed that accompanying pictograms did not significantly improve assessment of abdominal pain symptoms. However, the use of pictograms did improve the evaluation of nausea and vomiting, especially for children between 8 and 12 years of age. Therefore, we advise HCPs to use these pictograms in this setting during consultations.

Second, minimal invasive laboratory tests, such as blood parameters (hemoglobin (Hb), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), celiac disease screening and fecal calprotectin can be determined.[12,13] However, it is unknown whether fecal calprotectin may be best used as an additive biomarker or if it can be replaced by certain blood parameters (Hb, CRP, ESR). Therefore, in **chapter 2,** we retrospectively investigated the additional value of a 'full screening workup' (Hb, CRP, ESR, celiac disease screening, fecal calprotectin, and *G lamblia*) compared with a 'limited workup' without the most often used blood parameters (Hb, CRP, ESR), when discriminating a functional from an organic cause in children with chronic abdominal pain. In this retrospective cohort study, hospital charts of 853 children (aged 4–18 years) with abdominal pain for >2 months were included in analysis. 751 children had a functional cause for their abdominal pain, 102 children an organic disorder. We concluded that a 'limited diagnostic workup' with celiac disease screening, fecal calprotectin, and testing for *G lamblia* in the case of diarrhea, is equally accurate compared with a 'full screening workup' when blood parameters are added. However, caution should be taken not to miss extraintestinal infections. Furthermore, the accuracy of both workups further improved in the presence of ≥1 alarm symptoms. Though, before our suggested strategy may be adopted in clinical practice, further research should be performed, ideally in a large prospective cohort study.

PART II – Management: Psychosocial

Psychosocial interventions such as cognitive behavioral therapy (CBT) and hypnotherapy have proven to be successful in the management of FAPDs in childhood.[12]

However, it remains unavailable for many children, since costs are high, it is time-consuming and there is a the lack of well-trained child-hypnotherapists. Therefore, we previously researched the efficacy of home-based standardized audio hypnosis exercises with compact disc (CD) and demonstrated that it is non-inferior to individual hypnotherapy (iHT) by a therapist in the treatment of pediatric FAPDs.[14] Earlier research has shown that the beneficial effects of iHT are long lasting. However, the long-term effects of standardized hypnosis recordings were unknown. Therefore, in **chapter 3**, we conducted a follow-up study to investigate the long-term effects of standardized-hypnosis-recordings at home in comparison to iHT. 227 out of 250 (91%) children from our previous randomized controlled trial (RCT) completed this study. We found that 80% of children in the CD group and 86.6% of children in the iHT group reported adequate relief of their abdominal complaints at 6-year follow-up. These results support the future implementation of this widely available, easy-to-use, and cost-effective home-treatment in daily practice, and should be reimbursed by health insurance companies. Currently, online packages with the five HT recordings as used in the original RCT, together with a manual and instruction video, are available in Dutch, English and Spanish.[15–17]

In **chapter 4** we performed a systematic review on psychosocial interventions in children with FAPDs. In total, 33 studies on CBT, educational support, yoga, hypnotherapy and relaxation were included. From these results, we concluded that CBT and hypnotherapy may be considered as good treatment options for pediatric FAPDs. Future studies should consider the role of targeted interventions (i.e., combination of therapies) for susceptible children, and address quality issues to enhance the overall certainty of the results.

PART III – Management: Dietary and Pharmacological

Various dietary and pharmacological interventions have been suggested to improve symptoms of children with FAPDs. In **chapter 5** we performed a systematic review to determine the efficacy and safety of dietary interventions in children with FAPDs. 12 articles were included, comprising interventions on fibers, FODMAP diet, fructans, fructose-restricted diet, prebiotic (inulin), serum-derived bovine immunoglobulin, and vitamin D supplementation. Based on this review, we found some beneficial effects for the use of soluble fibers for the treatment of IBS with constipation in children. Furthermore, soluble fibers are easy available, low in cost, and safe in use.

In **chapter 6** we systematically reviewed the efficacy and safety of pharmacological interventions in children with FAPDs. 17 articles were included, and investigated the efficacy and safety of antispasmodics, antidepressants, antibiotics, antihistaminic, antiemetic, histamine-2-receptor antagonist, 5-HT4-receptor agonist, melatonin, and buspirone. Agents such as antispasmodics or antidepressants can be discussed in daily practice because of their favorable treatment outcomes and lack of important side effects. However, based on the current evidence it is not possible to recommend any specific pharmacologic agent for the treatment of any of the different pediatric FAPDs.

Both systematic reviews clearly reveal the lack of high-quality, placebo-controlled intervention trials, which are highly needed to improve clinical management.

PART IV – Shared Decision Making and Core Outcome Set

Shared decision making (SDM) in pediatrics aims to encourage HCPs to include children (aged 4-18 years) and their parents in decision-making, to improve quality of care and patient satisfaction, and reduce costs.[18–25] The *'3 Good Questions'* (*3GQ*) program was successfully implemented in adult healthcare to increase SDM, and therefore these *3GQ* have been adapted to a child version by the Dutch Child and Hospital Foundation and NVK for similar purposes.[26] To determine the feasibility of these *3GQ* in pediatric medicine, we performed a pilot study in **chapter 7**. We included 282 children (aged 10-18 years) at four pediatric outpatient clinics in the Netherlands. Half of the children received the intervention (i.e., *3GQ*) and the other half represented the control group. We found that the *3GQ* created awareness towards the possibility for children to ask questions. Furthermore, the use of the *3GQ* led to more SDM. The majority of children indicated to have heard of the *3GQ* program and would recommend the intervention to other children. However, only a few children used the *3GQ* during consultation. Therefore, it is necessary to further explore the implementation of the *3GQ* program at national level as a simple way for HCPs and children to share decisions in practice.

In therapeutic intervention trials for pediatric FAPDs, ways to define, report and measure study outcomes vary widely.[7,27–30] To inform clinical practice, future intervention trials should measure outcomes that are considered important to patients and parents and be useful to HCPs. '*Core outcome sets*' (COSs) have been proposed to ensure reporting consistency. A COS represents the agreed minimum

set of outcomes that should be measured and reported in clinical trials in a certain area.[7,31,32] In **chapter 8,** we therefore developed a COS, using a two-round Delphi technique, for clinical studies assessing FAPDs in children. 150 HCPs from over 30 countries, 100 parents and 50 children with a FAPD diagnosis (from Belgium, Italy, the Netherlands, Australia and Sri Lanka) were asked to list up outcomes that they considered important in FAPD treatment. *'Adequate relief*', *'anxiety/depression'*, *'defecation pattern'* (disease specific, IBS), *'pain intensity*', *'pain frequency'*, *'quality of life'*, *'school attendance'* and *'adverse events'* were included in the final COS. We suggest these 8 core outcomes should be minimally measured in clinical studies assessing pediatric FAPDs. Implementation of this COS is likely to increase comparison between studies and may thus provide future recommendations to improve treatment of FAPDs in children.

REFERENCES

1. Hyams, J. S. *et al.* Childhood functional gastrointestinal disorders: Child/adolescent. *Gastroenterology* 150, 1456–1468e2 (2016).
2. Korterink, J. J., Diederen, K., Benninga, M. A. & Tabbers, M. M. Epidemiology of Pediatric Functional Abdominal Pain Disorders: A Meta-Analysis. *PLoS One* 10, e0126982 (2015).
3. Rajindrajith, S. & Devanarayana, N. M. Subtypes and Symptomatology of Irritable Bowel Syndrome in Children and Adolescents: A School-based Survey Using Rome III Criteria. *J. Neurogastroenterol. Motil.* 18, 298–304 (2012).
4. Youssef, N. N., Murphy, T. G., Langseder, A. L. & Rosh, J. R. Quality of Life for Children With Functional Abdominal Pain: A Comparison Study of Patients' and Parents' Perceptions. *Pediatrics* 117, 54–59 (2006).
5. Varni, J. W. *et al.* Health-Related Quality of Life in Pediatric Patients with Functional and Organic Gastrointestinal Diseases. *J. Pediatr.* 166, 85–90.e2 (2015).
6. Drossman, D. A. Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 150, 1262–1279e2 (2016).
7. Zeevenhooven, J., Timp, M. L., Singendonk, M. M. J., Benninga, M. A. & Tabbers, M. M. Definitions of Pediatric Functional Abdominal Pain Disorders and Outcome Measures: A Systematic Review. *J. Pediatr.* 212, 52–59.e16 (2019).
8. Delp, C. & Jones, J. Communicating information to patients: the use ofcartoon illustrations to improvecomprehension of instructions. *Acadenuc Emerg. Med.* 3, 264–270 (1996).
9. Tack, J. *et al.* The use of pictograms improves symptom evaluation by patients with functional dyspepsia. *Aliment. Pharmacol. Ther.* 40, 523–530 (2014).
10. Zeng-Treitler, Q., Kim, H. & Hunter, M. Improving patient comprehension and recall of discharge instructions by supplementing free texts with pictographs. *AMIA Annu. Symp. Proc.* 849–853 (2008).
11. Morrow, D. G., Hier, C. M., Menard, W. E. & Von Leirer, O. Icons improve older and younger adults' comprehension of medication information. *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.* 53, (1998).
12. Thapar, N. *et al.* Paediatric functional abdominal pain disorders. *Nat. Rev. Dis. Prim.* 6, 89 (2020).
13. Tabbers, M. M., Rexwinkel, R. & de Bruijn, C. M. A. Guideline on Functional Abdominal Pain in Children [NVK Richtlijn Functionele Buikpijn bij Kinderen]. *NVK* (2022). Available at: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=189104128&tagtitles=Maag-Darm-Leverziekten%252b(MDL)%2CSociale%252ben%252bPsychosociale%252bkindergeneeskunde. (Accessed: 20th November 2022)
14. Rutten, J. M. T. M. *et al.* Home-based hypnotherapy self-exercises vs individual hypnotherapy with a therapist for treatment of pediatric irritable bowel syndrome, functional abdominal pain, or functional abdominal pain syndrome a randomized clinical trial. *JAMA Pediatr.* 171, 470–477 (2017).
15. Hypnosebijbuikpijn. Available at: https://hypnosebijbuikpijn.nl. (Accessed: 24th November 2022.
16. hypnosis4abdominalpain. Available at: https://hypnosis4abdominalpain.com. (Accessed 24th November, 2022).
17. Hipnosis dolor abdominal. Available at: http://hipnosisdolorabdominal.com. (Accessed 24th November, 2022).
18. Stichting kind&ziekenhuis. Available at: https://www.jadokterneedokter.nl/. (Accessed: 14th December 2022)

19. Charles, C., Gafni, A. & Whelan, T. Revisiting the shared treatment decision-making model. *Soc. Sci. Med.* 49, 651–61 (1999).
20. Charles, C., Gafni, A. & Whelan, T. Shared decision-making in the medical encounter: What does it mean? (Or it takes, at least two to tango). *Soc. Sci. Med.* 44, 681–692 (1997).
21. Makoul, G. & Clayman, M. L. An integrative model of shared decision making in medical encounters. *Patient Educ. Couns.* 60, 301–312 (2006).
22. Gabe, J., Olumide, G. & Bury, M. 'It takes three to tango': A framework for understanding patient partnership in paediatric clinics. *Soc. Sci. Med.* 59, 1071–1079 (2004).
23. Oshima Lee, E. & Emanuel, E. Shared Decision Making to Improve Care and Reduce Costs. *N. Engl. J. Med.* 368, 4–6 (2013).
24. Arterburn, D. *et al.* Introducing decision aids at group health was linked to sharply lower hip and knee surgery rates and costs. *Health Aff.* 31, 2094–2104 (2012).
25. Stacey, D. *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst. Rev.* 1–242 (2017). doi:10.1002/14651858.CD001431.pub5.www.cochranelibrary.com
26. Garvelink, M. M. *et al.* Implementation of the three good questions—A feasibility study in Dutch hospital departments. *Heal. Expect.* 22, 1272–1284 (2019).
27. Sinha, I. P., Gallagher, R., Williamson, P. R. & Smyth, R. L. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials* 13, 103 (2012).
28. Singendonk, M. M. J. *et al.* Variations in Definitions and Outcome Measures in Gastroesophageal Reflux Disease : A Systematic Review. 140, (2017).
29. Kapadia, M. Z. *et al.* A Core Outcome Set for Children With Feeding Tubes and Neurologic Impairment: A Systematic Review. *Pediatrics* 138, e20153967–e20153967 (2016).
30. Kuizenga-Wessel, S. *et al.* Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. *BMJ Paediatr. Open* 0, e000017 (2017).
31. Boers, M. *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J. Clin. Epidemiol.* 67, 745–753 (2014).
32. Williamson, P. R. *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 13, 132 (2012).

GENERAL DISCUSSION

In this thesis, we aimed to provide a clinical overview – *from diagnosis to management* – in pediatric functional abdominal pain disorders (FAPDs). This discussion will focus on recommendations for diagnostic and management strategies, on challenges in research and future perspectives, all with a particular emphasis on irritable bowel syndrome (IBS) and functional abdominal pain – not otherwise specified (FAP-NOS).

Recommendations for clinical management

The optimal treatment strategy for diagnosing and treating children with pediatric FAPDs is not known. An individualized approach to management, using a stepwise approach, is the foundation of managing these disorders. This includes minimal investigations (**chapter 2**), making a positive diagnosis, and the involvement of patients and families in shared decision making (SDM).[1] Based on family's beliefs, the treatment of comorbid symptoms (such as bloating, constipation, diarrhea and nausea), and the published evidence as underlined in this thesis, we propose a tailor-made approach for each patient. We think it is preferable to discuss both non-pharmacological and pharmacological options during consultation together with patients and parents or caregivers (**Figure 1**). The '*3 Good Questions*' may be helpful for children to ask questions, to get information from their healthcare professional (HCP), and to improve participation in SDM (**chapter 7**). The importance of SDM should therefore be emphasized, to assist children (aged 4-18 years), and their parents, to make well informed decisions.

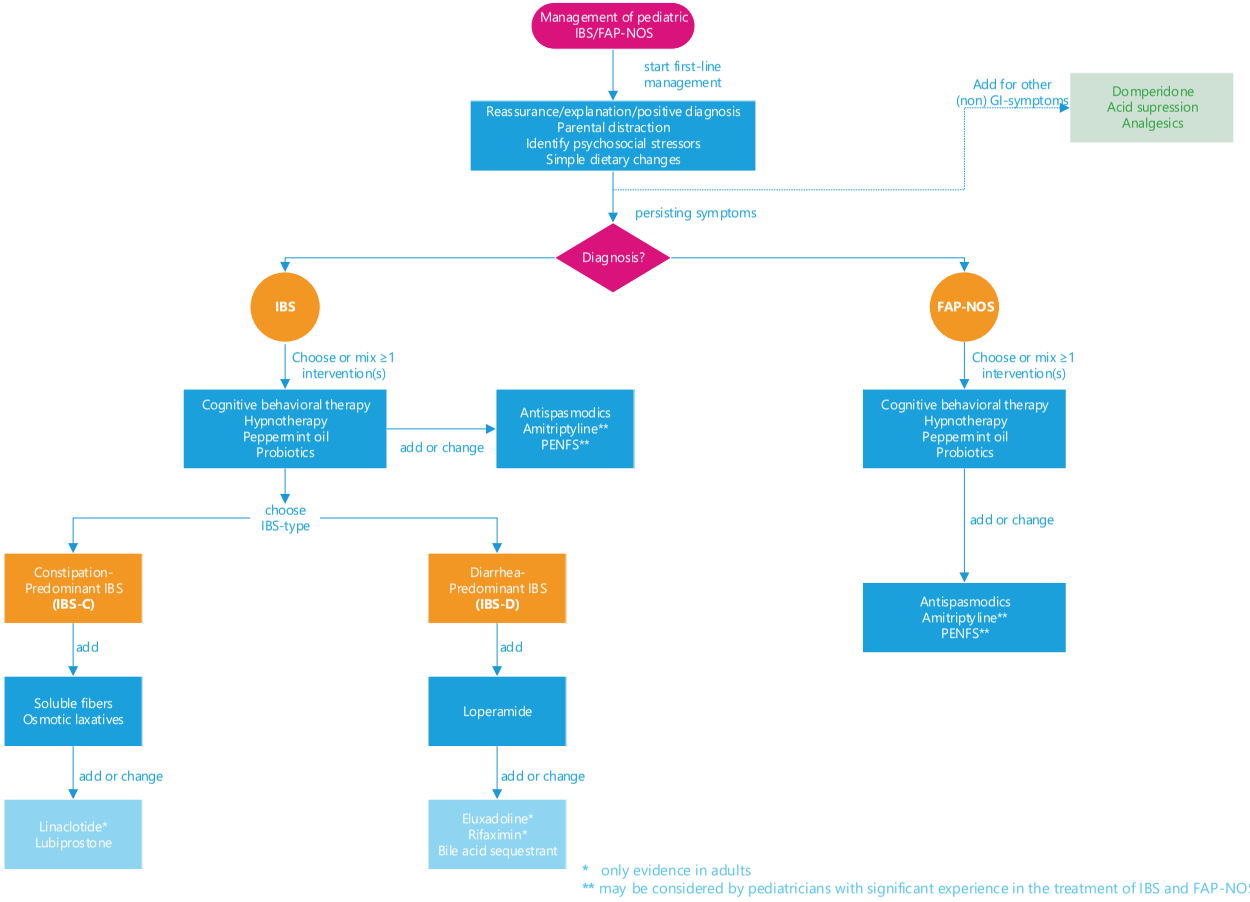

Figure 1. *Proposed Flow Diagram of Treatment. Reproduced and adapted with permission from Springer Nature. Rexwinkel, R., Vlieger, A.M., Saps, M. et al. A therapeutic guide on pediatric irritable bowel syndrome and functional abdominal pain–not otherwise specified. Eur J Pediatr 181, 2603–2617 (2022).*

First-line management consists of validation, a proper explanation of the diagnosis according to the biopsychosocial model, and identification of potential stress factors.[1,2] Schechter et al provided guidelines to improve patient-provider relationship, also known as the '*golden half hour*'.[1] The importance of the '*golden half hour*' should be acknowledged, which can improve long-term prognosis.[1] In addition, it is important to understand the expectations, anxiety and perspectives from both child and parents to optimize treatment.[1] Furthermore, it can be helpful to explain that the pain is likely caused by a combination of several factors, using metaphors like that all tires of a car must work to be able to move.[1] Simple dietary advices, such as adequate fiber intake, and limited ingestion of food products containing high levels of lactose, sucrose or fructose (with respect to bloating) should be given. In addition, education on the importance of parental distraction (i.e., not actively discussing the pain) should be included in initial treatment.[2,3] The use of standardized materials during consultation, for example a (digital) presentation or short video clips, may help in providing uniform information based on scientific evidence, to both child and parent(s) during the first step of treatment. This might especially be helpful for HCPs not specialized in childhood FAPD treatment.

If these steps do not result in adequate improvement, psychological interventions, especially cognitive behavioral therapy (CBT) and hypnotherapy, could be proposed given that these have proven to be the most effective therapies with long-term benefits (**chapter 4**). However, CBT and hypnotherapy are not easily available because of a lack of allied HCPs and lack of insurance coverage. New developments include the delivery of online psychological therapies.[4–9] In **chapter 3** we showed that the beneficial effects of home-based standardized audio hypnosis exercises with compact disc (CD) are long lasting. On the other hand, some children and their parents might prefer pharmacological therapy (i.e., peppermint oil) or a combination of non-pharmacological and pharmacological interventions. It is important to underline that data on the actual efficacy of the latter is limited, although a combination of different treatments could be proposed. The use of probiotics (i.e., *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri*) may have some benefit, as they have shown to reduce pain frequency and provide better symptom relief in children with FAPDs.[10] Studies in adults with IBS reported positive treatment effects of both antispasmodics and antidepressants.[11–14] In **chapter 6** we showed that antispasmodics (i.e., peppermint oil or mebeverine) or

antidepressants (i.e., amitriptyline) may be discussed in clinical practice because of their favorable treatment outcomes and the lack of important side effects, although high-quality randomized controlled trials (RCTs) in children are lacking. Despite this, 62% of pediatric gastroenterologists in North America reported prescribing TCAs for FGIDs.[15] Also, mebeverine is often prescribed in children, and appears even in the top four most commonly used drugs for complaints concerning the gastrointestinal tract.[16] Only one RCT have been conducted on the efficacy and safety of mebeverine in children with abdominal pain, but these results should be interpreted with caution given the low dose used and short duration of treatment. Currently, a multicenter, randomized, placebo-controlled trial on mebeverine is ongoing in children with IBS and FAP-NOS (EUCTR2015-003293-32-NL).

The predominant type of IBS should be determined, namely with constipation (IBS- C) or diarrhea (IBS- D), to offer appropriate management strategies. As described in **chapter 5**, soluble fibers can be considered for the treatment of IBS-C, due to their favorable treatment outcomes, low costs, lack of reported side effects and easy availability. Also laxatives, such as polyethylene glycol 3350 (PEG), are commonly used in the treatment for IBS-C.[17,18] New agents such as linaclotide and lubiprostone are highly recommended for the treatment of adults with IBS-C.[19,20] However, these agents are not approved yet for use in children with either IBS-C or functional constipation. A retrospective study in the USA found that around 40% of children with IBS-C reported benefit (defined as a positive clinical response) of linaclotide use, but 30% of children developed diarrhea as a side effect.[21] The use of lubiprostone in children with IBS-C are giving conflicting results.[22–24] Loperamide may be considered in children with IBS-D for symptomatic treatment.[18,25,26] In adolescents with IBS-D, the efficacy of eluxadoline is currently assessed (NCT03339128). For children with persistent and troublesome IBS-D symptoms, newer modalities such as bile acid sequestrans and rifaxamin may be beneficial but more research is necessary.[26–29]

Although abdominal pain is the major clinical manifestation of FAPDs, other symptoms are also common due to the multifactorial nature of these disorders. Special notice should be made to non-abdominal pain symptoms, which are associated with an increase in abdominal pain and (related) complaints and are present in nearly three-quarter of children, resulting in poor prognosis.[30–33] These comprise symptoms such as back-, chest-, extremity- (arms and legs), and joint pain and headache, and could be treated with analgesics, such as

non-steroidal anti-inflammatory drugs or paracetamol, for a short duration of time.[33] Furthermore, for comorbid symptoms as dyspepsia and nausea, which are experienced by 50% of children multiple times a week, acid suppression and domperidone can be used as symptomatic treatment.[34-40] The use of pictograms during consultation may improve the evaluation of these symptoms (**chapter 1**).

A multidisciplinary, tailor-made approach to provide support is idealistic, but unfortunately in many practices not available or possible. Having said this, the majority of children can successfully be treated with first-line management in primary care setting, emphasizing the importance of this '*golden half hour*'. If first-line management fails, referral to a secondary or tertiary hospital is necessary.

For future research, the ultimate goal would be to develop and validate a prediction model to assess the most appropriate treatment option for each patient. The first step in this process is to identify potential prognostic factors, ideally from large longitudinal observational cohorts. National or international collaborations for pediatric FAPD research can facilitate this process.

Challenges in clinical trials

The lack of high-quality RCTs could be considered as one of the main causes that limits evidence-based recommendations for pediatric FAPD management. Primarily is this related to the low number of RCTs conducted in this area with usually small sample sizes, and secondly because of challenges in performing clinical intervention trials. Finally, across trials, there is a variety of definitions and outcome measures used, including different instruments to measure these outcomes.

First, the barriers to complete an appropriate double-blind, placebo-controlled trial in children are extensive, through difficulties in complex ethical and institutional review boards issues, long informed consent processes, limited funding, lost-to-follow-up and missing data.[41-44] Besides, pediatricians may have concerns about participating in clinical trials because of its time investment and the infringement on their daily practice. Moreover, it appears that pediatricians often have a preference for a particular treatment, despite the lack of scientific evidence for this approach.[45,46] Altogether, this may negatively affect participation of children in clinical studies, and is also an obstacle to obtain an adequate sample size. In addition, parents are often hesitant to enroll their children in RCTs due to

the possibility of receiving a placebo or an agent with unknown treatment benefit, or to be exposed to potential, unidentified, side effects.[47–50] Therefore, multicenter RCTs should be proposed, to recruit a large number of children. However, the downside of multicenter trials is that this also require local review approval, which may lead to high costs, increased and inefficient administrative burden and, consequently, delaying start of study.[51,52] Good Clinical Practice (CGP)-compliant infrastructure in pediatric hospitals is considered as one of the conditions to successfully conduct a clinical trial.[53] This may be accomplished by having an experienced trial coordinator in the study team, who understands the complexity of managing intervention trials in children, and who can ease trial conduct and recruitment.[46,50,54] For example, an extremely important, but underestimated and time-consuming task, is to send reminders to participants to fill in daily diaries or questionnaires, to minimize the risk of missing data and recall bias.[55]

Second, there is a major heterogeneity in study designs, definitions, outcome measures, patient characteristics, treatment durations and follow-up, which hampers the comparability of published study results and performing meta-analysis.[56] To overcome the latter, we developed an international core outcome set (COS) for therapeutic intervention trials in pediatric FAPDs in **chapter 8**.

The next step is determining *how to measure* these outcome measures, by identifying which measurement instruments are therefore needed and validated in order to permit successful implementation.[57,58] *Abdominal pain intensity* and *frequency* were rated as the most important outcomes in this COS, and recommended as primary outcome measure by a subcommittee for clinical FAPD trials of the Rome Foundation and the Pediatric Committee of the European Medicines Agency (EMA).[59] Earlier research found that 11 different measurement instruments were used to measure *pain intensity* and *frequency*. However, in order to achieve uniformity, it is important to recommend one single instrument.[56] This committee advises to assess *abdominal pain* with (electronic) daily dairies for at least 7 days at two time points (7 days before start of the trial; and 7 days at the end of the trial while still on medication).[60–62] This in order to minimize recall bias.[55]

The rising question is whether *abdominal pain* is the outcome measuring 'the full experienced symptom package', since FAPDs are multifactorial conditions. Therefore, another proposed primary outcome measure, from our COS and the Rome foundation, is *adequate relief* of symptoms. This outcome measure was

traditionally measured in IBS clinical trials, but is not recommended by the EMA and FDA.[59,63–66] *Adequate relief* lets the patient focus on its own reference system of improvement, by subjectively combining all patient's relevant symptoms. The effect of FAPD symptoms on an individual level, independently of symptom severity, are hereby reported which is crucial when evaluating treatment response.[67,68] This is comparable with clinical practice, where *adequate relief* of symptoms is often used to describe outcomes of given treatements.[64] Because of the fluctuations in symptoms that occur naturally over time, symptoms need to be assessed over several days to weeks to ensure representative data. However, issues arise as duration of data collection, and optimal timing for recall. Yet, in daily clinical practice, treatment efficacy is constantly based on recall bias, often for a longer period of time. A recent systematic review showed that for children ≥8 years old, a recall period from the past 14 days is reliable.[69] Thus there is a need for proper validation of both an abdominal pain diary, as well as for the outcome measure *adequate relief*, to perform future intervention trials.

The acceptability of Patient Reported Outcome Measures (PROMs) (willingness to complete a measure) is, alongside of the feasibility of PROMS (ability to complete a measure), crucial for engagement in pediatric research and for the provision of reliable and valid results.[70,71] Research has shown that the acceptability of children in research is expanding by using visual appealing measures, such as the faces scales, preferred in a 3-point response scale (for children ≥7 years) and computerized format.[69] The latter will lead to a decrease in missing data.[69] However, missing data and lost-to-follow-up in pediatric research are mainly due to a lack of motivation, different expectations of treatment efficacy and the fact that participating in research is a considerable time investment.[72] All in all, missing data leads to reminders, leading to a higher percentage of recall bias.[55]

Future research should focus on reasons why children are not completing their PROMs, preferably in a qualitative study. Also, there is an increased interest in involving children and parents in the earliest stage of study development: design and recruitment of trial, and consent. It is important to identify potential barriers or priorities for children and parents in not contributing to all aspects of the study.[73] However, this requires both an investment of time and financial resources.

RCTs are the gold standard for effectiveness research, however, the main problem with RCTs is that they are performed under strict controlled conditions, such

as restrictive inclusion and exclusion criteria and measurement moments.[72] This may affect their external validity, that consequently hampers generalizability to the children seen in everyday practice.[74,75] It is important to recruit children with different age, ethnicity and gender.[42] Furthermore, the choice of control group (i.e., a placebo, a waiting list or care as usual) has been shown to influence the effect size of the intervention. Due to the high placebo response in pediatric FAPDs, it is therefore difficult to identify the true effect size.[76,77] Different factors contribute to the placebo effect, including the Hawthorne effect (i.e., effect of being evaluated and observed), the natural course of the disease, regression towards the mean and contextual factors (i.e., conditioning and expectations).[78] Contextual factors are known as the 'true placebo effect'.[79–81] To discriminate between the 'true placebo effect' and the other factors, it is necessary to conduct an RCT with different comparators, such as a placebo arm versus a waiting list or a no treatment group.[77,82,83] However, because of various ethical difficulties and the lack of blinding to treatment allocation, these designs need further evaluation.[78,84] A proposed solution to improve the external validity of pediatric FAPD trials could be the addition of large prospective observational studies, and compare these data with results from particular RCTs.[85,86] This may be accomplished by the development of large patient registries, by creating an international database for pediatric FAPDs.[87–92] Another advantage of such an international database is the opportunity to compare and correct for patient characteristics from participants form different countries. This is important because the organization of healthcare differs worldwide, and consequently affects which initial treatment will be given. For example, children from the USA are mostly evaluated in primary care setting by their own pediatrician.[93] In contrast in the Netherlands, children need to consult a general practitioner first in order to receive a referral letter to a pediatrician in secondary care.[94] This could create a difference in treatment chronicity and thereby influences prognosis. Also, the long-term effects of treatment, adverse events and prognosis can be studied worldwide. To our knowledge, no such consortium initiative have been developed for pediatric FAPDs.

In conclusion, we suggest to perform minimal diagnostic testing and to use a stepwise individualized approach for the management of children with FAPDs. After first-line management, both non-pharmacological and pharmacological interventions should be discussed together with patients and their parents. For future research, we recommend to involve children and their parents in

the earliest stage of the study development and to perform research in a CGP-compliant infrastructure, ideally by having an experienced trial coordinator. The use of the COS for pediatric FAPDs in multicenter RCTs and observational studies will provide comparable results that is necessary to guide adequate clinical management in the future. Furthermore, the selection and validation of the most appropriate primary outcome measure and measurement instrument is essential. The ultimate goal would be to develop and validate a prediction model to assess the most appropriate treatment option for each patient. The use of large international longitudinal observational cohorts for pediatric FAPD research can facilitate this process.

REFERENCES

1. Schechter, N. L., Coakley, R. & Nurko, S. The Golden Half Hour in Chronic Pediatric Pain-Feedback as the First Intervention. *JAMA Pediatr.* 175, 7–8 (2021).
2. Rexwinkel, R., Vlieger, A. M., Saps, M., Tabbers, M. M. & Benninga, M. A. A therapeutic guide on pediatric irritable bowel syndrome and functional abdominal pain-not otherwise specified. *Eur. J. Pediatr.* 181, 2603–2617 (2022).
3. Thapar, N. *et al.* Paediatric functional abdominal pain disorders. *Nat. Rev. Dis. Prim.* 6, 89 (2020).
4. Bonnert, M. *et al.* Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial. *Am. J. Gastroenterol.* 112, 152–162 (2017).
5. Sampaio, F. *et al.* Cost-effectiveness of internet-delivered cognitive-behavioural therapy for adolescents with irritable bowel syndrome. *BMJ Open* 9, e023881 (2019).
6. Nieto, R., Boixadós, M., Ruiz, G., Hernández, E. & Huguet, A. Effects and Experiences of Families Following a Web-Based Psychosocial Intervention for Children with Functional Abdominal Pain and Their Parents: A Mixed-Methods Pilot Randomized Controlled Trial. *J. Pain Res.* 12, 3395–3412 (2019).
7. Walker, L. S. *et al.* Internet-delivered cognitive behavioral therapy for youth with functional abdominal pain: a randomized clinical trial testing differential efficacy by patient subgroup. *Pain* (2021).
8. van Tilburg, M. A. L. *et al.* Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. *Pediatrics* 124, e890-7 (2009).
9. Rutten, J. M. T. M. *et al.* Home-based hypnotherapy self-exercises vs individual hypnotherapy with a therapist for treatment of pediatric irritable bowel syndrome, functional abdominal pain, or functional abdominal pain syndrome a randomized clinical trial. *JAMA Pediatr.* 171, 470–477 (2017).
10. Wallace, C., Gordon, M., Sinopoulou, V. & Akobeng, A. Probiotics for management of functional abdominal pain disorders in children. *Cochrane Database Syst. Rev.* (2021). doi:10.1002/14651858
11. Black, C. J. *et al.* Efficacy of soluble fibre, antispasmodic drugs, and gut–brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol. Hepatol.* 5, 117–131 (2020).
12. Ford, A. C. *et al.* Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am. J. Gastroenterol.* 109, 1350–1365 (2014).
13. Ruepert, L. *et al.* Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst. Rev.* 2011, (2011).
14. Daniluk, J., Malecka-Wojciesko, E., Skrzydlo-Radomanska, B. & Rydzewska, G. The Efficacy of Mebeverine in the Treatment of Irritable Bowel Syndrome-A Systematic Review. *J. Clin. Med.* 11, (2022).
15. Schurman, J. V, Hunter, H. L. & Friesen, C. A. Conceptualization and treatment of chronic abdominal pain in pediatric gastroenterology practice. *J. Pediatr. Gastroenterol. Nutr.* 50, 32–37 (2010).
16. Sturkenboom, M. C. J. M. *et al.* Drug use in children: cohort study in three European countries. *BMJ* 337, a2245 (2008).

17. Khoshoo, V., Armstead, C. & Landry, L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 23, 191–196 (2006).
18. Tabbers, M. M., Rexwinkel, R. & de Bruijn, C. M. A. Guideline on Functional Abdominal Pain in Children [NVK Richtlijn Functionele Buikpijn bij Kinderen]. *NVK* (2022). Available at: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=189104128&tagtitles=Maag-Darm-Leverziekten%252b(MDL)%2CSociale%252ben%252bPsychosociale%252bkindergeneeskunde. (Accessed: 20th November 2022)
19. Shah, E. D., Kim, H. M. & Schoenfeld, P. Efficacy and Tolerability of Guanylate Cyclase-C Agonists for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation: A Systematic Review and Meta-Analysis. *Am. J. Gastroenterol.* 113, 329–338 (2018).
20. Chang, L. *et al.* AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation. *Gastroenterology* 163, 118–136 (2022).
21. Baaleman, D. F. *et al.* The Use of Linaclotide in Children with Functional Constipation or Irritable Bowel Syndrome: A Retrospective Chart Review. *Paediatr. Drugs* 23, 307–314 (2021).
22. Hyman, P. E., Di Lorenzo, C., Prestridge, L. L., Youssef, N. N. & Ueno, R. Lubiprostone for the treatment of functional constipation in children. *J. Pediatr. Gastroenterol. Nutr.* 58, 283–291 (2014).
23. Benninga, M., Hussain, S. & Sood, M. Efficacy and safety of lubiprostone in children with functional constipation: a multicenter, randomized, placebo-controlled, double-blind pivotal study. *Gastroenterology* 154, S559-60 (abstr) (2018).
24. Benninga, M. A. *et al.* Lubiprostone for Pediatric Functional Constipation: Randomized, Controlled, Double-Blind Study With Long-term Extension. *Clin. Gastroenterol. Hepatol.* 20, 602-610.e5 (2022).
25. Lacy, B. E. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. *Int. J. Gen. Med.* 9, 7–17 (2016).
26. Lembo, A. *et al.* AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea. *Gastroenterology* 163, 137–151 (2022).
27. Camilleri, M. *et al.* Effect of colesevelam on faecal bile acids and bowel functions in diarrhoea-predominant irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 41, 438–448 (2015).
28. Camilleri, M. Bile Acid diarrhea: prevalence, pathogenesis, and therapy. *Gut Liver* 9, 332–339 (2015).
29. Vijayvargiya, P. *et al.* Bile Acid Deficiency in a Subgroup of Patients With Irritable Bowel Syndrome With Constipation Based on Biomarkers in Serum and Fecal Samples. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* 16, 522–527 (2018).
30. Rabbitts, J. A., Holley, A. L., Groenewald, C. B. & Palermo, T. M. Association Between Widespread Pain Scores and Functional Impairment and Health-Related Quality of Life in Clinical Samples of Children. *J. pain* 17, 678–684 (2016).
31. Skrove, M., Romundstad, P. & Indredavik, M. S. Chronic multisite pain in adolescent girls and boys with emotional and behavioral problems: the Young-HUNT study. *Eur. Child Adolesc. Psychiatry* 24, 503–515 (2015).
32. Maixner, W., Fillingim, R. B., Williams, D. A., Smith, S. B. & Slade, G. D. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. *J. pain* 17, T93–T107 (2016).

33. Chumpitazi, B. P. *et al.* Multisite Pain Is Highly Prevalent in Children with Functional Abdominal Pain Disorders and Is Associated with Increased Morbidity. *J. Pediatr.* 236, 131–136 (2021).
34. Arts, E., Anthoni, H., de Roy, G., D'Hollander, J. & Verhaegen, H. Domperidone in the Treatment of Dyspepsia: A Double-Blind Placebo-Controlled Study. *J. Int. Med. Res.* 7, 158–161 (1979).
35. Milo, R. Use of the peripheral dopamine antagonist, domperidone, in the management of gastrointestinal symptoms in patients with irritable bowel syndrome. *Curr. Med. Res. Opin.* 6, 577–584 (1980).
36. Van de Mierop, L., Rutgeerts, L., Van den Langenbergh, B. & Staessen, A. Oral domperidone in chronic postprandial dyspepsia. A double-blind placebo-controlled evaluation. *Digestion* 19, 244–250 (1979).
37. Sarin, S. K., Sharma, P., Chawla, Y. K., Gopinath, P. & Nundy, S. Clinical trial on the effect of domperidone on non-ulcer dyspepsia. *Indian J. Med. Res.* 83, 623–628 (1986).
38. Karunanayake, A., Devanarayana, N. M., De Silva, A., Gunawardena, S. & Rajindrajith, S. Randomized Controlled Clinical Trial on Value of Domperidone in Functional Abdominal Pain in Children. *J. Pediatr. Gastroenterol. Nutr.* 66, 725–731 (2018).
39. Kovacic, K., Williams, S., Li, B. U. K., Chelimsky, G. & Miranda, A. High prevalence of nausea in children with pain-associated functional gastrointestinal disorders: are Rome criteria applicable? *J. Pediatr. Gastroenterol. Nutr.* 57, 311–315 (2013).
40. Russell, A. C., Stone, A. L. & Walker, L. S. Nausea in Children With Functional Abdominal Pain Predicts Poor Health Outcomes in Young Adulthood. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* 15, 706–711 (2017).
41. Leibson, T. & Koren, G. Informed consent in pediatric research. *Paediatr. Drugs* 17, 5–11 (2015).
42. Roth-Cline, M., Gerson, J., Bright, P., Lee, C. S. & Nelson, R. M. Ethical considerations in conducting pediatric research. *Handb. Exp. Pharmacol.* 205, 219–244 (2011).
43. Klassen, T. P., Hartling, L., Craig, J. C. & Offringa, M. Children are not just small adults: the urgent need for high-quality trial evidence in children. *PLoS Med.* 5, e172 (2008).
44. Bourgeois, F. T. *et al.* Pediatric versus adult drug trials for conditions with high pediatric disease burden. *Pediatrics* 130, 285–292 (2012).
45. Spriggs, M. & Caldwell, P. H. Y. The ethics of paediatric research. *J. Paediatr. Child Health* 47, 664–667 (2011).
46. Caldwell, P. H. Y., Butow, P. N. & Craig, J. C. Pediatricians' attitudes toward randomized controlled trials involving children. *J. Pediatr.* 141, 798–803 (2002).
47. Joseph, P. D., Craig, J. C. & Caldwell, P. H. Y. Clinical trials in children. *Br. J. Clin. Pharmacol.* 79, 357–369 (2015).
48. Connolly, M. R. *et al.* Design and Reporting Characteristics of Clinical Trials of Select Chronic and Recurrent Pediatric Pain Conditions: An Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks Systematic Review. *J. pain* 20, 394–404 (2019).
49. Shilling, V. & Young, B. How do parents experience being asked to enter a child in a randomised controlled trial? *BMC Med. Ethics* 10, 1 (2009).
50. Caldwell, P. H. Y., Murphy, S. B., Butow, P. N. & Craig, J. C. Clinical trials in children. *Lancet (London, England)* 364, 803–811 (2004).
51. Green, L. A., Lowery, J. C., Kowalski, C. P. & Wyszewianski, L. Impact of Institutional Review Board Practice Variation on Observational Health Services Research. *Health Serv. Res.* 41, 214–230 (2006).
52. Ravina, B., Deuel, L., Siderowf, A. & Dorsey, E. R. Local institutional review board (IRB) review of a multicenter trial: Local costs without local context. *Ann. Neurol.* 67, 258–260 (2010).

53. Barker, C. I. S. *et al.* Pharmacokinetic studies in children: recommendations for practice and research. *Arch. Dis. Child.* 103, 695–702 (2018).
54. Caldwell, P. H. y, Butow, P. N. & Craig, J. C. Parents' attitudes to children's participation in randomized controlled trials. *J. Pediatr.* 142, 554–559 (2003).
55. Chogle, A. *et al.* Accuracy of pain recall in children. *J. Pediatr. Gastroenterol. Nutr.* 55, 288–291 (2012).
56. Zeevenhooven, J., Timp, M. L., Singendonk, M. M. J., Benninga, M. A. & Tabbers, M. M. Definitions of Pediatric Functional Abdominal Pain Disorders and Outcome Measures: A Systematic Review. *J. Pediatr.* 212, 52–59.e16 (2019).
57. Prinsen, C. A. C. *et al.* How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" – a practical guideline. *Trials* 17, 449 (2016).
58. Gorst, S. L. *et al.* Methods used in the selection of instruments for outcomes included in core outcome sets have improved since the publication of the COSMIN/COMET guideline. *J. Clin. Epidemiol.* 125, 64–75 (2020).
59. Saps, M. *et al.* Recommendations for pharmacological clinical trials in children with irritable bowel syndrome: the Rome foundation pediatric subcommittee on clinical trials. *Neurogastroenterol. Motil.* 28, 1619–1631 (2016).
60. Bailey, B., Daoust, R., Doyon-Trottier, E., Dauphin-Pierre, S. & Gravel, J. Validation and properties of the verbal numeric scale in children with acute pain. *Pain* 149, 216–221 (2010).
61. Bailey, B., Bergeron, S., Gravel, J. & Daoust, R. Comparison of four pain scales in children with acute abdominal pain in a pediatric emergency department. *Ann. Emerg. Med.* 50, 379–83, 383.e1–2 (2007).
62. von Baeyer, C. L. *et al.* Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain* 143, 223–227 (2009).
63. Trentacosti, A. M., He, R., Burke, L. B., Griebel, D. & Kennedy, D. L. Evolution of clinical trials for irritable bowel syndrome: issues in end points and study design. *Am. J. Gastroenterol.* 105, 731–735 (2010).
64. Camilleri, M. *et al.* Comparison of adequate relief with symptom, global, and responder endpoints in linaclotide phase 3 trials in IBS-C. *United Eur. Gastroenterol. J.* 3, 53–62 (2015).
65. U.S. Department of Health and Human Services Food and Drug Administration Center for Evaluation and Research (CDER). *Guidance for Industry: Irritable Bowel Syndrome-Clinical Evaluation of Drugs for Treatment.* (2012).
66. Committee for Medicinal Products for Human Use. *Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome*. *European Medicines Agency* 44, (2014).
67. Camilleri, M. *et al.* Primary Endpoints for Irritable Bowel Syndrome Trials: A Review of Performance of Endpoints. *Clin. Gastroenterol. Hepatol.* 5, 534–540 (2007).
68. Creed, F. *et al.* Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. *Ann. Intern. Med.* 134, 860–68 (2001).
69. Coombes, L. *et al.* Enhancing validity, reliability and participation in self-reported health outcome measurement for children and young people: a systematic review of recall period, response scale format, and administration modality. *Qual. life Res. an Int. J. Qual. life Asp. Treat. care Rehabil.* 30, 1803–1832 (2021).
70. Bevans, K. B., Riley, A. W., Moon, J. & Forrest, C. B. Conceptual and methodological advances in child-reported outcomes measurement. *Expert Rev. Pharmacoecon. Outcomes Res.* 10, 385–396 (2010).

71. De Vet, H. C. W., Terwee, C. B., Mokkink, L. B. & Knol, D. L. *Measurement in medicine: a practical guide*. (Cambridge university press, 2011).

72. Kennedy-Martin, T., Curtis, S., Faries, D., Robinson, S. & Johnston, J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 16, 495 (2015).

73. Carpenter, D., Gonzalez, D., Retsch-Bogart, G., Sleath, B. & Wilfond, B. Methodological and Ethical Issues in Pediatric Medication Safety Research. *Pediatrics* 140, (2017).

74. Sniderman, A. D., LaChapelle, K. J., Rachon, N. A. & Furberg, C. D. The necessity for clinical reasoning in the era of evidence-based medicine. *Mayo Clin. Proc.* 88, 1108–1114 (2013).

75. Rothwell, P. M. External validity of randomised controlled trials: 'to whom do the results of this trial apply?'. *Lancet (London, England)* 365, 82–93 (2005).

76. Hoekman, D. R. *et al.* The Placebo Response in Pediatric Abdominal Pain-Related Functional Gastrointestinal Disorders: A Systematic Review and Meta-Analysis. *J. Pediatr.* 182, 155-163.e7 (2017).

77. Finniss, D. G., Kaptchuk, T. J., Miller, F. & Benedetti, F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 375, 686–695 (2010).

78. Kaptchuk, T. J., Hemond, C. C. & Miller, F. G. Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ* 370, m1668 (2020).

79. Kirsch, I. The placebo effect revisited: lessons learned to date. *Complement. Ther. Med.* 21, 102–104 (2013).

80. Elsenbruch, S. & Enck, P. Placebo effects and their determinants in gastrointestinal disorders. *Nat. Rev. Gastroenterol. Hepatol.* 12, 472–485 (2015).

81. Benninga, M. A. & Mayer, E. A. The Power of Placebo in Pediatric Functional Gastrointestinal Disease. *Gastroenterology* 137, 1207–1210 (2009).

82. Kaptchuk, T. J. *et al.* Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 336, 999–1003 (2008).

83. von Wernsdorff, M., Loef, M., Tuschen-Caffier, B. & Schmidt, S. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. *Sci. Rep.* 11, 3855 (2021).

84. Nurko, S. *et al.* Open label placebo for children with functional abdominal pain and irritable bowel syndrome: A randomized crossover trial. *JAMA Pediatr.* (2021).

85. Saarijärvi, M., Wallin, L., Moons, P., Gyllensten, H. & Bratt, E.-L. Factors affecting adolescents' participation in randomized controlled trials evaluating the effectiveness of healthcare interventions: the case of the STEPSTONES project. *BMC Med. Res. Methodol.* 20, 205 (2020).

86. Fraser, J., Steele, N., Al Zaman, A. & Yule, A. Are patients in clinical trials representative of the general population? Dose intensity and toxicities associated with FE100C-D chemotherapy in a non-trial population of node positive breast cancer patients compared with PACS-01 trial group. *Eur. J. Cancer* 47, 215–220 (2011).

87. Ruperto, N. & Martini, A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). *Arch. Dis. Child.* 96, 596–601 (2011).

88. Bosch, X. *et al.* Causes of ineligibility in randomized controlled trials and long-term mortality in patients with non-ST-segment elevation acute coronary syndromes. *Int. J. Cardiol.* 124, 86–91 (2008).

89. Crandall, W. V *et al.* Improved outcomes in a quality improvement collaborative for pediatric inflammatory bowel disease. *Pediatrics* 129, e1030-41 (2012).

90. Paediatric European Network for the Treatment of AIDS (PENTA). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500007138.pdf. (Accessed: 6th December 2022).

91. Children's Cancer and Leukaemia Group (CCLG). Available at: https://www.cclg.org.uk/. (Accessed: 6th December 2022).

92. The Children's Oncology Group (COG). Available at: https://childrensoncologygroup.org/. (Accessed: 6th December 2022).

93. Rice, T., Rosenau, P., Unruh, L. Y. & Barnes, A. J. *United States: Health System Review. Health systems in transition* 22, (2020).

94. Kroneman, M. *et al. Netherlands: Health System Review. Health systems in transition* 18, (2016).

NEDERLANDSE SAMENVATTING

Chronische buikpijn komt veel voor bij kinderen en kan een organische oorzaak, zoals inflammatoire darmziekten (IBD) of glutenallergie (coeliakie) of een functionele oorzaak hebben. Bij 90% van de kinderen met chronische buikpijn is er sprake van een functionele oorzaak voor de pijn, er wordt dan gesproken van functionele buikpijn (internationale term '*functional abdominal pain disorders*' (FAPDs)).[1,2] Dit komt wereldwijd bij 13.5% van de kinderen voor.[2] Functionele buikpijn is een overkoepelende term voor 4 buikpijnsyndromen en wordt bij kinderen volgens de Rome IV criteria op basis van symptomen ingedeeld in: (1) functionele dyspepsie, (2) prikkelbare darmsyndroom (PDS), (3) abdominale migraine en (4) functionele buikpijn – niet anders gespecificeerd.[1,2] In het vervolg van deze samenvatting zal de term *'functionele buikpijn'* gebruikt worden om te verwijzen naar bovengenoemde 4 buikpijnsyndromen.

De diagnose functionele buikpijn wordt gesteld op basis van klachten die kinderen ervaren.[3] Om aan de diagnose te voldoen, moeten kinderen minstens 1 keer per week klachten hebben gedurende een periode van tenminste 2 maanden. Daarnaast moeten deze klachten in het geval van PDS ook gepaard gaan met veranderingen in het ontlastingspatroon, zoals diarree of obstipatie.[1,4] De impact van functionele buikpijn is aanzienlijk; de kwaliteit van leven van kinderen met functionele buikpijn is in vergelijking met gezonde kinderen gemiddeld een stuk slechter en er is een hoge mate van schoolverzuim.[5,6] De impact blijft onverminderd groot, des te meer omdat de oorzaak van functionele buikpijn vaak niet geheel bekend is en het derhalve onduidelijk is wat als meest optimale behandeling kan dienen. Er is uitgebreid wetenschappelijk onderzoek gedaan naar behandeling van functionele buikpijn bij kinderen, maar vanwege de heterogeniteit en de lage kwaliteit van deze studies, blijft het moeilijk om specifieke aanbevelingen te doen.[7] Daarnaast kan het moeilijk zijn voor kinderen met functionele buikpijn om hun klachten goed te omschrijven. In het kader van dit proefschrift zijn daarom een aantal studies uitgevoerd die tot doel hebben om de kwaliteit van zorg voor kinderen met functionele buikpijn te verbeteren en betere *evidence-based* besluitvorming mogelijk te maken.

In **deel I** van dit proefschrift focussen we ons op het verbeteren van het stellen van de **diagnose** en onderzoeken we of het gebruik van pictogrammen tijdens het consult bij kinderen met functionele buikpijn helpt om hun klachten beter te

omschrijven. In **deel II en III** van dit proefschrift richten we ons op verschillende **behandelingsstrategieën**. De behandeling van functionele buikpijn bestaat uit uitleg, geruststelling, veranderingen in leefstijl, niet-medicamenteuze behandeling zoals psychosociale interventies, waaronder cognitieve gedragstherapie (CGT) en hypnotherapie, en medicatie. Om de effectiviteit en veiligheid van de meest gebruikte behandelingen te onderzoeken, beschrijven we de resultaten van drie systematische reviews naar psychosociale-, dieet- en medicamenteuze behandelingen bij kinderen met functionele buikpijn. **Deel IV** van dit proefschrift beschrijft eerst haalbaarheid, dan implementatie van een **gezamenlijke besluitvoering** interventie bij kinderen en de ontwikkeling van een '***core outcome set***' (COS), een basisset van uitkomstmaten die in toekomstig (behandel)onderzoek gemeten en gerapporteerd dienen te worden.

DEEL I – Diagnose

De eerste stap om de diagnose functionele buikpijn bij kinderen te stellen is een uitgebreide anamnese en lichamelijk onderzoek om mogelijke alarmsymptomen, zoals een positieve familieanamnese (IBD of coeliakie), ongewild gewichtsverlies of bloedverlies uit het maag-darmkanaal te vinden.[1] Tijdens dit consult kan het voor kinderen lastig zijn om de klachten goed te beschrijven, wat de communicatie tussen kind, ouder(s) en zorgverlener kan belemmeren. Het gebruik van pictogrammen (zogenoemde '*Patient Reported Outcome Measures*' (*PROMs*)) tijdens het consult kan kinderen met functionele buikpijn helpen om de klachten beter te omschrijven.[8–11] In **hoofdstuk 1** hebben we daarom het gebruik van deze pictogrammen geëvalueerd bij kinderen met functionele buikpijn. 144 kinderen (8-18 jaar oud) uit twee academische ziekenhuizen (Amsterdam en Leuven) werden geïncludeerd in dit vragenlijstonderzoek. Uit het onderzoek kon worden geconcludeerd dat het gebruik van de pictogrammen voornamelijk bij kinderen van 8 tot 12 jaar goed werkt bij het omschrijven van de klachten die samenhangen met misselijkheid en braken. Bij andere klachten zagen we dat het gebruik van de pictogrammen geen significante verbetering bij het omschrijven van de klachten oplevert. Gezien de positieve resultaten, adviseren wij aan zorgverleners om deze pictogrammen bij de beschrijving van de klachten misselijkheid en braken te gebruiken.

De volgende stap bij het stellen van de diagnose functionele buikpijn is het verrichten van aanvullende onderzoeken, zoals bloedonderzoek (hemoglobine, C-reactief proteïne (CRP), bezinking), screening op coeliakie en fecesonderzoek.[12,13]

Door middel van het bloedonderzoek en het fecesonderzoek wordt gekeken of er mogelijk een organische oorzaak is voor de buikklachten. In de feces wordt daarvoor de hoeveelheid fecaal calprotectine bepaald, een ontstekingsparameter. Het is echter niet bekend of de bepaling van fecaal calprotectine alleen voldoende is voor het uitsluiten van een organische oorzaak voor de buikpijn. Als dat zo is, zou het bloedonderzoek dus achterwege gelaten kunnen worden. In **hoofdstuk 2** hebben wij daarom retrospectief onderzocht wat de toegevoegde waarde is van een 'volledig onderzoek' (bloedonderzoek, coeliakiescreening, fecaal calprotectine en *Gardia Lamblia*) in vergelijking met een 'beperkt onderzoek' (zonder bloedonderzoek), om een onderscheid te maken tussen een functionele en organische oorzaak van chronische buikpijn. In dit retrospectieve cohort onderzoek werden de gegevens uit patiëntendossiers van 853 kinderen (4-18 jaar oud) met chronische buikpijn gedurende een periode van tenminste 2 maanden geanalyseerd. Bij 751 kinderen was sprake van een functionele oorzaak voor hun buikpijn, bij 102 kinderen ging het om een organische oorzaak. Uit deze studie kan worden geconcludeerd dat het bloedonderzoek achterwege gelaten zou kunnen worden in de diagnostiek voor chronische buikpijn bij kinderen. Er moet echter voor worden gewaakt dat extra-intestinale infecties niet worden gemist. De accuratesse van beide onderzoeken verbeterde nog meer bij aanwezigheid van 1 of meer alarmsymptomen. Voordat de resultaten van deze retrospectieve studie in de klinische praktijk toegepast kunnen worden, moet er meer onderzoek worden verricht. Idealiter in een groot prospectief cohort onderzoek.

DEEL II – Behandeling: Psychosociaal

Wetenschappelijk onderzoek heeft aangetoond dat psychosociale behandelingen zoals cognitieve gedragstherapie (CGT) en hypnotherapie succesvol zijn in de behandeling van functionele buikpijn bij kinderen.[12] Echter zijn deze behandelingen voor veel kinderen niet beschikbaar vanwege de hoge kosten en een gebrek aan opgeleide (kinder)hypnotherapeuten. Bovendien zijn de behandelingen zeer tijdsintensief. 5 jaar geleden hebben we in een groot multicenter onderzoek laten zien dat in de behandeling van kinderen met functionele buikpijn, thuisbehandeling met een audio-CD niet-inferieur is aan individuele hypnotherapie bij een hypnotherapeut.[14] De langetermijneffecten van individuele hypnotherapie zijn eerder (al) onderzocht, met goed resultaat. Echter, de langetermijneffecten van gestandaardiseerde hypnose-opnamen (via een audio- cd) zijn onbekend. Daarom hebben we in **hoofdstuk 3**

een follow-up onderzoek gedaan naar de langetermijneffecten van hypnotherapie met het gebruik van hypnose-oefeningen op audio-CD in de thuissituatie in vergelijking met individuele hypnotherapie door een therapeut. 227 van de 250 (91%) kinderen uit ons eerder gerandomiseerd onderzoek hebben deelgenomen. Na gemiddeld 6 jaar follow-up bleek 80% in de audio-CD-groep en 86.6% in de individuele hypnotherapie groep adequate verlichting van de buikpijnklachten te hebben. We concludeerden dat de gunstige effecten van zowel thuisbehandeling met audio-CD als individuele hypnotherapie bij een hypnotherapeut langdurig zijn. Behandeling met hypnotherapie oefeningen op audio-CD lijkt daarmee een eenvoudige, algemeen beschikbare en kosteneffectieve thuisbehandeling voor (in) de dagelijkse praktijk. Inmiddels is deze thuisbehandeling met hypnose oefeningen online verkrijgbaar in het Nederlands, Engels en Spaans.[15–17]

In **hoofdstuk 4** hebben we de resultaten van een systematische review naar de effectiviteit van psychosociale behandelingen bij kinderen met functionele buikpijn beschreven. We includeerden 33 studies over CGT, hypnotherapie, yoga, biofeedback en educatieve begeleiding. Uit deze studies blijkt dat CGT en hypnotherapie een waardevolle toevoeging zijn aan de behandeling van functionele buikpijn bij kinderen. Toekomstig onderzoek zou zich kunnen richten op de toegevoegde waarde van meer adequate behandelingen (d.w.z. een combinatie van verschillende therapieën) en kan meerwaarde opleveren door te focussen op de opzet en uitvoering.

DEEL III - Behandeling: Dieet en Medicatie

Er kunnen verschillende dieet- en medicamenteuze behandelingen overwogen worden om de symptomen van functionele buikpijn bij kinderen te verminderen. In **hoofdstuk 5** hebben we de resultaten van een systematische review naar de werkzaamheid en veiligheid van verschillende dieet- en voedingsbehandelingen bij kinderen met functionele buikpijn beschreven. We includeerden 12 onderzoeken naar vezels, FODMAP-dieet, fructanen, fructosebeperkt dieet, prebioticum (inuline), serum-afgeleide runderimmunoglobuline en vitamine D-suppletie. Uit deze onderzoeken konden we concluderen dat alleen het gebruik van wateroplosbare vezels effectief kunnen zijn in de behandeling bij kinderen met PDS (het obstipatie type). Wateroplosbare vezels zijn ook makkelijk te gebruiken en te verkrijgen en er zijn geen bijwerkingen (van) bekend.

In **hoofdstuk 6** hebben we de werkzaamheid en veiligheid van medicamenteuze behandelingen bij kinderen met functionele buikpijn systematisch onderzocht. 17 onderzoeken werden geïncludeerd met de volgende medicamenteuze behandelingen: spasmolytica, antidepressiva, antibiotica, antihistaminica, anti-emetica, histamine-2-receptorantagonisten, 5-HT4-receptoragonisten, melatonine en buspiron. We concludeerden dat in de dagelijkse praktijk behandeling met spasmolytica of antidepressiva vanwege de gunstige behandeluitkomsten en het ontbreken van ernstige bijwerkingen kunnen worden overwogen. Op basis van het huidige wetenschappelijk onderzoek is het echter niet mogelijk om een specifiek medicamenteuze behandeling aan te bevelen.

Beide systematische reviews tonen echter aan dat de kwaliteit van de studies vaak niet voldoende is. Er is een gebrek aan placebo-gecontroleerde medicamenteuze- en dieet-interventie studies van hoge kwaliteit, die nodig zijn om de behandeling van functionele buikpijn bij kinderen te verbeteren.

DEEL IV – Gezamenlijke Besluitvorming en Core Outcome Set

Aanbevolen wordt om kinderen (4-18 jaar oud) te betrekken bij de besluitvorming over een onderzoek of behandeling (gezamenlijke besluitvorming/'*shared decision making*').[18] Dit kan de kwaliteit van de zorg verbeteren.[19–25] De '*3 Goede Vragen*'-campagne is door Patiëntenfederatie Nederland en de Federatie Medisch Specialisten ontwikkeld om gezamenlijke besluitvorming te bevorderen en wordt met succes bij volwassenen toegepast in de klinische praktijk.[26] Daarom zijn de *3 Goede Vragen* voor dit onderzoek door Stichting Kind en Ziekenhuis en de NVK speciaal aangepast voor kinderen, zodat kinderen zelfstandig in gesprek kunnen gaan met hun behandelend arts en zelf ook vragen kunnen stellen. Om te onderzoeken of de *3 Goede Vragen*-methode ook bij kinderen goed werkt, hebben wij in **hoofdstuk 7** een pilotstudie uitgevoerd. Wij includeerden 282 kinderen (10-18 jaar oud) in vier ziekenhuizen in Nederland. De helft van de kinderen ontving de interventie (d.w.z. de *3 Goede Vragen*), de andere helft vormde de controlegroep. Uit het onderzoek bleek dat de *3 Goede vragen* ervoor zorgden dat kinderen zich meer bewust zijn van de mogelijkheid om vragen te stellen. Het gebruik van de *3 Goede Vragen* leidde tot meer gezamenlijke besluitvorming. Het merendeel van de kinderen gaf aan van de *3 Goede Vragen* gehoord te hebben en het aan te bevelen aan andere kinderen. Echter heeft maar een klein deel van de kinderen de *3 Goede Vragen* gebruikt tijdens het gesprek met de arts. Hoe dat komt, is onduidelijk. Het is daarom noodzakelijk om

de implementatie van de *3 Goede Vragen*-campagne op landelijk niveau verder te onderzoeken. De *3 Goede Vragen* hebben de potentie om in de klinische praktijk op een eenvoudige manier gezamenlijke beslissingen te kunnen nemen.

Het vergelijken van verschillende ((niet-)medicamenteuze) onderzoeken bij kinderen met functionele buikpijn is ingewikkeld, omdat er veel verschillende manieren zijn om functionele buikpijn te definiëren en veel verschillende uitkomstmaten om de effectiviteit van een behandeling te bepalen.[7,27–30] Om de dagelijkse klinische praktijk te informeren moeten toekomstige onderzoeken uitkomsten meten die belangrijk zijn voor zowel zorgverleners als voor kinderen en hun ouders. Dit wordt ook wel een *'core outcome set'* (COS) genoemd. Een COS is een gestandaardiseerde set van uitkomstmaten die in toekomstig (behandel) onderzoek gemeten en gerapporteerd dient te worden.[7,31,32] In **hoofdstuk 8** hebben wij een COS voor functionele buikpijn bij kinderen ontwikkeld met behulp van de Delphi-techniek. In 2 rondes werden 150 zorgverleners uit meer dan 30 landen, 100 ouders en 50 kinderen met functionele buikpijn (uit België, Italië, Nederland, Australië en Sri Lanka) gevraagd om uitkomstmaten te noemen die zij belangrijk vinden in de behandeling. *'Adequate verlichting van klachten'*, *'angst/depressie*', *'ontlastingspatroon'* (ziekte-specifiek voor PDS), *'pijnintensiteit'* (sterkte van de pijn), *'pijnfrequentie', 'kwaliteit van leven', 'schoolverzuim*' en *'bijwerkingen'* zijn de 8 uitkomstmaten die op basis van dit onderzoek werden opgenomen in de uiteindelijke COS. Wij stellen voor deze uitkomstmaten te meten in toekomstig (behandel) onderzoek naar functionele buikpijn bij kinderen. De COS heeft de potentie om de heterogeniteit van studies te verminderen, waardoor het gemakkelijker wordt om studieresultaten te vergelijken en zodoende de toekomstige behandeling van functionele buikpijn bij kinderen te verbeteren.

Conclusie

Samenvattend zijn in dit proefschrift een achttal studies uitgevoerd waarvan de resultaten kunnen dienen als ondersteuning om de diagnostiek en behandeling te verbeteren en het gezamenlijke besluitvormingsproces te bevorderen, met als doel om de kwaliteit van zorg en toekomstig onderzoek voor kinderen met functionele buikpijn te verbeteren. In het hoofdstuk ***'general discussion'*** worden op basis van de resultaten uit dit proefschrift aanbevelingen gedaan voor de behandeling van functionele buikpijn bij kinderen (***Figure 1****. Proposed Flow Diagram of Treatment*) en worden zowel uitdagingen als aanbevelingen voor het toekomstige onderzoek besproken.

REFERENTIES

1. Hyams, J. S. *et al.* Childhood functional gastrointestinal disorders: Child/adolescent. *Gastroenterology* 150, 1456-1468e2 (2016).
2. Korterink, J. J., Diederen, K., Benninga, M. A. & Tabbers, M. M. Epidemiology of Pediatric Functional Abdominal Pain Disorders: A Meta-Analysis. *PLoS One* 10, e0126982 (2015).
3. Drossman, D. A. Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 150, 1262-1279e2 (2016).
4. Rajindrajith, S. & Devanarayana, N. M. Subtypes and Symptomatology of Irritable Bowel Syndrome in Children and Adolescents: A School-based Survey Using Rome III Criteria. *J. Neurogastroenterol. Motil.* 18, 298–304 (2012).
5. Varni, J. W. *et al.* Health-Related Quality of Life in Pediatric Patients with Functional and Organic Gastrointestinal Diseases. *J. Pediatr.* 166, 85-90.e2 (2015).
6. Youssef, N. N., Murphy, T. G., Langseder, A. L. & Rosh, J. R. Quality of Life for Children With Functional Abdominal Pain: A Comparison Study of Patients' and Parents' Perceptions. *Pediatrics* 117, 54–59 (2006).
7. Zeevenhooven, J., Timp, M. L., Singendonk, M. M. J., Benninga, M. A. & Tabbers, M. M. Definitions of Pediatric Functional Abdominal Pain Disorders and Outcome Measures: A Systematic Review. *J. Pediatr.* 212, 52-59.e16 (2019).
8. Delp, C. & Jones, J. Communicating information to patients: the use ofcartoon illustrations to improvecomprehension of instructions. *Acadenuc Emerg. Med.* 3, 264–270 (1996).
9. Tack, J. *et al.* The use of pictograms improves symptom evaluation by patients with functional dyspepsia. *Aliment. Pharmacol. Ther.* 40, 523–530 (2014).
10. Zeng-Treitler, Q., Kim, H. & Hunter, M. Improving patient comprehension and recall of discharge instructions by supplementing free texts with pictographs. *AMIA Annu. Symp. Proc.* 849–853 (2008).
11. Morrow, D. G., Hier, C. M., Menard, W. E. & Von Leirer, O. Icons improve older and younger adults' comprehension of medication information. *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.* 53, (1998).
12. Thapar, N. *et al.* Paediatric functional abdominal pain disorders. *Nat. Rev. Dis. Prim.* 6, 89 (2020).
13. Tabbers, M. M., Rexwinkel, R. & de Bruijn, C. M. A. Guideline on Functional Abdominal Pain in Children [NVK Richtlijn Functionele Buikpijn bij Kinderen]. *NVK* (2022). Available at: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=189104128&tagtitles=Maag-Darm-Leverziekten%252b(MDL)%2CSociale%252ben%252bPsychosociale%252bkindergeneeskunde. (Accessed: 20th November 2022)
14. Rutten, J. M. T. M. *et al.* Home-based hypnotherapy self-exercises vs individual hypnotherapy with a therapist for treatment of pediatric irritable bowel syndrome, functional abdominal pain, or functional abdominal pain syndrome a randomized clinical trial. *JAMA Pediatr.* 171, 470–477 (2017).
15. Hypnose bij buikpijn. Available at: https://hypnosebijbuikpijn.nl. (Accessed: 24th November 2022.
16. hypnosis 4 abdominal pain. Available at: https://hypnosis4abdominalpain.com. (Accessed 24th November, 2022).
17. Hipnosis dolor abdominal. Available at: http://hipnosisdolorabdominal.com. (Accessed 24th November, 2022).
18. Stichting kind&ziekenhuis. Available at: https://www.jadokterneedokter.nl/. (Accessed: 14th December 2022)

19. Charles, C., Gafni, A. & Whelan, T. Shared decision-making in the medical encounter: What does it mean? (Or it takes, at least two to tango). *Soc. Sci. Med.* 44, 681–692 (1997).
20. Charles, C., Gafni, A. & Whelan, T. Revisiting the shared treatment decision-making model. *Soc. Sci. Med.* 49, 651–61 (1999).
21. Makoul, G. & Clayman, M. L. An integrative model of shared decision making in medical encounters. *Patient Educ. Couns.* 60, 301–312 (2006).
22. Gabe, J., Olumide, G. & Bury, M. 'It takes three to tango': A framework for understanding patient partnership in paediatric clinics. *Soc. Sci. Med.* 59, 1071–1079 (2004).
23. Oshima Lee, E. & Emanuel, E. Shared Decision Making to Improve Care and Reduce Costs. *N. Engl. J. Med.* 368, 4–6 (2013).
24. Arterburn, D. *et al.* Introducing decision aids at group health was linked to sharply lower hip and knee surgery rates and costs. *Health Aff.* 31, 2094–2104 (2012).
25. Stacey, D. *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst. Rev.* 1–242 (2017). doi:10.1002/14651858.CD001431.pub5.www.cochranelibrary.com
26. Garvelink, M. M. *et al.* Implementation of the three good questions—A feasibility study in Dutch hospital departments. *Heal. Expect.* 22, 1272–1284 (2019).
27. Sinha, I. P., Gallagher, R., Williamson, P. R. & Smyth, R. L. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials* 13, 103 (2012).
28. Singendonk, M. M. J. *et al.* Variations in Definitions and Outcome Measures in Gastroesophageal Reflux Disease : A Systematic Review. 140, (2017).
29. Kapadia, M. Z. *et al.* A Core Outcome Set for Children With Feeding Tubes and Neurologic Impairment: A Systematic Review. *Pediatrics* 138, e20153967–e20153967 (2016).
30. Kuizenga-Wessel, S. *et al.* Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. *BMJ Paediatr. Open* 0, e000017 (2017).
31. Boers, M. *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J. Clin. Epidemiol.* 67, 745–753 (2014).
32. Williamson, P. R. *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 13, 132 (2012).