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Home-based guided hypnotherapy for children with functional abdominal pain and irritable bowel syndrome in primary care: study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Children often present to primary care with functional abdominal pain (FAP) or irritable bowel syndrome (IBS), and around half of the children still have abdominal complaints one year later. Hypnotherapy is an evidence-based treatment in specialist care, whereas it lacks evidence in primary care. Therefore, this study will investigate the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care.

Methods and analysis: We report the design of a pragmatic, randomised controlled trial among children aged 7–17 years diagnosed with FAP or IBS by their general practitioner (GP), who will be assessed over 12 months. The control group will receive care as usual by their GP (e.g. communication, education and reassurance), while the intervention group will receive care as usual plus 3 months of home-based guided hypnotherapy via a website. The primary outcome will be the proportion of children with adequate relief from abdominal pain/discomfort at 12 months, analysed on an intention-to-treat basis. Secondary outcomes include adequate pain relief at 3 and 6 months, together with pain/discomfort severity, pain frequency and intensity, daily functioning and impact on function, anxiety and depression, pain beliefs, sleep disturbances, school absence, somatisation, and health care use and costs. We must include 200 children to determine a 20% difference in those with adequate relief (55% control vs. 75% intervention).

Ethics and dissemination: The Medical Ethics Review Committee of the University Medical Center Groningen, the Netherlands, approved this study (METc2020/237). The results will be disseminated to patients, GPs and other stakeholders via e-mail, a dedicated website, peer-reviewed publications and presentations at national and international conferences. We plan to collaborate with the Dutch Society of GPs to implement the results in clinical practice.

Registration details: The Dutch Trial Register: NL8500.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Early management of functional abdominal pain (FAP) and irritable bowel syndrome (IBS) through home-based guided hypnotherapy may prevent symptoms becoming chronic.
- Exercises are learnt using digital media (eHealth) and fit well with the target population of young, digitally skilled patients.
- Our pragmatic design has high external generalisability and will provide useful information on the (cost) effectiveness of home-based guided hypnotherapy in a real-world setting.
- The internal validity may be low due to a lack of blinding, with the potential that children in the control group will seek alternative treatment.

ABBREVATIONS

CAU	Care as usual
CSI	Children's Somatisation Inventory
EQ-5D-Y	EuroQol Five Dimensions Health Questionnaire Youth
FAP	Functional Abdominal Pain
GP	General practitioner
IBS	Irritable Bowel Syndrome
iMCQ	iMTA Medical Consumption Questionnaire
iPCQ	iMTA Productivity Cost Questionnaire
NHG	*Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
NRS	Numerical Rating Scale
PBQ	Pain Beliefs Questionnaire
QoL	Quality of Life
RCADS	Revised Anxiety and Depression Scale
REDCap	Research Electronic Data Capture
ZelfHy	*ZelfHypnose*; self-hypnosis

INTRODUCTION

Background and rationale

Children often present to primary care with functional gastrointestinal symptoms, such as functional abdominal pain (FAP) or irritable bowel syndrome (IBS), that cannot be explained by an organic condition and risk becoming chronic.[1-4] These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.[5,6] However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.[7,8] Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,[9] adequate early treatment in primary care could reduce symptoms and the need for secondary care referral.

The general practitioner (GP) functions as a gatekeeper to specialist care in the Netherlands, similar to systems in Canada and the UK.[10] Therefore, all children with FAP or IBS usually present first in primary care, where a GP determines the diagnosis by excluding organic causes through clinical history-taking and physical examination.[11-13] The Dutch Society of GPs (*Nederlands Huisartsen Genootschap;* NHG) guideline for FAP, which recommends good communication, education and reassurance, may not be sufficient for all children.[14,15] Around half of these children still report abdominal complaints after 1 year,[3] underlining the difficulty of treatment.

Children with FAP or IBS often receive psychosocial interventions in specialist paediatric care due to the strong association between functional symptoms and psychological factors (e.g. stress).[12,13,15-17] Hypnotherapy is one such option that involves a therapist inducing a hypnotic state by guiding a patient to respond to suggestions.[18-20] Studies measuring brain responses in adults with IBS show that hypnotherapy may influence gut motility and normalise visceral sensitivity,[21,22] but the mechanisms behind its effect on functional abdominal

symptoms are poorly understood. Nevertheless, research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.[18,19,23] Other research in children has proven the non-inferiority of home-based guided hypnotherapy to face-to-face therapist-guided hypnotherapy at 12 months (75% vs. 87% had adequate pain relief, respectively), though with less effectiveness for children who have long-term symptoms.[24] The use of hypnotherapy earlier in the course of symptoms could maximise its benefits, especially if delivered in primary care, but evidence of its (cost) effectiveness is lacking in this setting. Indeed, home-based guided hypnotherapy could improve how GPs manage children with FAP or IBS, potentially leading to a better prognosis, fewer unnecessary referrals and reduced costs.

Hypothesis

We hypothesise that, compared to care as usual (CAU) alone, home-based guided hypnotherapy plus CAU will be more (cost) effective for achieving adequate relief from abdominal pain and discomfort in children with FAP or IBS.

METHODS AND ANALYSIS

Study design

We present the ZelfHy (*ZelfHypnose*; self-hypnosis) study, a pragmatic randomised controlled trial designed to determine the (cost) effectiveness of home-based guided hypnotherapy plus CAU compared to CAU alone for children with FAP or IBS in primary care. Recruitment has already begun, with eligible children being randomised to either the intervention group or the control group and followed for 12 months (Figure 1). This protocol is reported according to the SPIRIT guidelines[25] and the extended CONSORT statement for pragmatic trials.[26]

Study population

The inclusion criteria are as follows: age 7–17 years; attending a GP with chronic gastrointestinal symptoms (e.g. recurrent abdominal pain for ≥2 months or ≥2 episodes in the

past 2 months); and GP-diagnosed FAP or IBS. Those with a concomitant organic gastrointestinal disease, abdominal symptoms treated by a paediatrician, mental retardation, psychotic disorders, those who have undergone hypnotherapy in the past year or have poor comprehension of the Dutch language, are excluded. Children who prefer not to randomise can choose to enter a parallel cohort study in which they complete the same questionnaires.

Recruitment

We invited GPs through either the Academic General Practitioner Development Network (AHON; *Academisch Huisarts Ontwikkel Netwerk*) or professional connections and asked them to recruit participants. Participating GPs inform eligible children about the trial and provide written information during their consultation. Additionally, GP assistants are performing retrospective searches in GP registration databases each month for potentially eligible children, using a search strategy based on International Classification of Primary Care codes (Supplement 1). Primary care practices in the Netherlands have been recruiting children since November 2020, aiming to complete recruitment by September 2023.

Slow recruitment by GPs to 1st July 2022 (only 30 children), led us to expand the routes to participation. We now provide information via schools, social media, local media (e.g. newspapers and radio) and different interest groups (e.g. for parents and IBS groups) to allow self-referral by interested children and/or parents via the study website. The research team then makes contact by telephone, sends the appropriate information and informed consent forms, and asks them to make an appointment with their GP.

Data collection

GPs check the eligibility criteria using specific forms, irrespective of the recruitment method, and send these to the research team. The research team sends the appropriate information and informed consent forms to children recruited via their GP. A researcher then contacts each child by phone to resolve any queries and complete the Rome IV Diagnostic Questionnaire (parent

version if <12 years, child version if ≥12 years).[27] The research team only sends the baseline questionnaires after obtaining written informed consent from the participant. After receiving the completed questionnaire, they randomise the participant and inform them of their allocation by phone. Follow-up questionnaires are sent at 3, 6 and 12 months. All questionnaires can be completed in around 30 minutes either on paper or via the REDCap (Research Electronic Data Capture) website.[28] REDCap sends automatic e-mail reminders after 7 and 14 days if the questionnaires are not completed. After 21 days, researchers remind the participants by phone and ask whether the child has experienced adequate relief from abdominal pain/discomfort (primary outcome). Despite the low risk of (severe) adverse events, we have accommodated spontaneous reporting. All study-related and participant information is stored securely at the study site in locked file cabinets that can only be accessed by the researchers.

Randomisation, allocation and blinding

We use a computer-generated 1:1 randomisation list with varying block sizes (4, 6 and 8) that includes stratification by age (<12 years or ≥12 years). An independent methodologist (M.R. de Boer, PhD) manages the randomisation list and treatment allocation. The nature of the intervention precludes blinding of the GPs, children, and parents, but researchers performing the statistical analyses will be blinded to group allocation.

Intervention

Care as usual

All children receive CAU by their GP according to the NHG guideline for abdominal pain in children,[14] offering communication, education and reassurance. The guideline advocates realistic treatment goals that focus on pain management, rather than pain resolution, and follow-up. Researchers provide all participating GPs with a quick reference card of the guideline highlights (Supplement 2).

Hypnotherapy by self-exercises

Children in the intervention group are asked to perform home-based guided hypnotherapy for 3 months, supplemented with CAU by their GP. Prior to starting the exercises, a researcher arranges an online video call with the child and parent(s) to explain hypnotherapy, how it can help reduce abdominal pain and how they can access the exercises. Additionally, the child and parent(s) are instructed not to discuss the pain anymore.[29]

We use an existing home-based guided hypnotherapy programme, as described elsewhere,[29] adjusted for this study. This comprises one breathing and progressive relaxation exercise and four visualisation exercises recorded by a hypnotherapist in a digital audio format (MP3). The language is adapted to the child's age, with one version each for children aged <12 years and ≥12 years. We include the instructions and exercises for both versions in a newly designed, responsive, login-protected website. Instructions are directly visible on the home page and vary each week. Children are asked to listen to the exercises at least five times per week, for 15–20 minutes per day, over 3 months. To improve compliance, they receive automatic e-mail reminders from the website after 14 and 28 days of inactivity.

Outcomes

Table 1 gives an overview of the outcome measures and covariates used in this study. The outcomes are based on a recommended set of variables for clinical trials of paediatric FAP disorders.[30] Demographic data are obtained from the inclusion form and outcomes are measured at baseline and at 3, 6 and 12 months' follow-up (T0, T1, T2 and T3, respectively). Parents complete the questionnaires for children aged <12 years, while children aged ≥12 years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

Table 1. Overview of outcome parameters and covariates

Primary outcome	**Source**	**T0**	**T1**	**T2**	**T3**
Adequate pain relief at 12 months	Binary yes/no question				x
Secondary outcomes					
Adequate pain relief at 3 and 6 months	Binary yes/no question		x	x	
Severity of pain/discomfort	NRS-11	x	x	x	x
Pain frequency and intensity	Abdominal pain diary	x	x	x	x
Daily functioning and impact	KIDSCREEN-52	x	x	x	x
Anxiety and depression	RCADS-25	x	x	x	x
Pain beliefs	PBQ	x	x	x	x
Sleep disturbances	Sleep Self Report	x	x	x	x
School absence	Study questionnaire**	x	x	x	x
Somatisation	CSI	x	x	x	x
Utility	EQ-5D-Y	x	x	x	x
Costs	Adjusted iPCQ & iMCQ Medical records	x	x	x	x
Evaluation of intervention					
Usage of intervention*	Study questionnaire**		x	x	x
Quality of exercises*	Study questionnaire**		x		
Covariates					
Age	Study inclusion form	x			
Severity of pain/discomfort	NRS-11	x			
Treatment expectations	Study questionnaire**	x			

*Only for intervention group.

**The study questionnaires were created specifically for this research.

Abbreviations: NRS-11, Numerical Rating Scale-11; RCADS-25, Revised Anxiety and Depression Scale-25; PBQ, Pain Beliefs Questionnaire; CSI, Children's Somatisation Inventory; EQ-5D-Y, EuroQol Five Dimensions Health Questionnaire Youth; iPCQ, iMTA Productivity Cost Questionnaire; iMCQ, iMTA Medical Consumption Questionnaire.

Primary outcome

The primary outcome is the proportion of children with adequate relief of abdominal pain/discomfort after 12 months. The child or parent(s) are asked whether relief from abdominal pain or discomfort has been adequate during the past week, compared to baseline, on a

dichotomous scale (yes/no). Self-reported adequate relief is a well validated outcome measurement in other trials of IBS treatment.[31]

Secondary outcomes

Adequate pain relief at 3 and 6 months

The proportion of children with adequate relief of abdominal pain/discomfort at 3 and 6 months will be assessed using the same dichotomous scale as the primary outcome.

Severity of pain/discomfort

The severity of abdominal pain and/or discomfort in the past week is assessed using a 11-point numerical rating scale (NRS-11) from 0 (no pain) to 10 (worst pain). This scale provides valid and reliable scores in children and adolescents with chronic pain.[32,33]

Pain intensity and frequency

Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,[33] as recommended and often used in other trials of childhood FAP or IBS.[29,33] Pain intensity is assessed using an affective facial pain scale,[34,35] where the faces range from showing no pain at all (score 0) to the most severe pain (score 3). Pain frequency is assessed by asking how long the pain lasted per day, ranging from no pain (score 0) to >2 hours (score 3). The frequency and intensity scores are then totalled for 7 days, giving total ranges of 0–21 per score.[24]

Quality of life

The KIDSCREEN-52 is a reliable and valid health-related QoL questionnaire that measures the impact of abdominal pain on daily functioning and QoL.[36-38] It comprises 52 items covering ten dimensions: physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, relations with parents and home life, social support and peers, school environment, social acceptance (bullying) and financial resources. Participants rate behaviour frequency or attitude intensity in the past week on 5-point Likert scales. Higher scores

correspond to better health-related QoL and well-being.

Anxiety and depression

Symptoms of anxiety and depression are assessed by a short version of the Revised Child Anxiety and Depression Scale (RCADS-25), which is a valid and reliable instrument in Dutch populations.[39] The child or parent indicates how often each of the 20 anxiety and 5 depression items applies to the child on 4-point scales from 0 (never) to 3 (always). Higher scores indicate more symptoms of anxiety and/or depression.

Pain beliefs

The paediatric Pain Beliefs Questionnaire (PBQ) includes 32 items that assess beliefs about abdominal pain.[40] Each item consists of a pain belief statement with responses that range from not true at all (score 0) to very true (score 4). The PBQ comprises three subscales: pain threat (20 items), problem-focused coping efficacy (6 items) and emotion-focused coping efficacy (6 items). A higher score on the pain threat scale indicates a stronger belief that their abdominal pain is a threat. Higher scores on both coping subscales indicate stronger beliefs in their ability to cope with pain using either problem-focused or emotion-focused strategies.

Sleep disturbances

Sleep disturbances are measured using three items from the Dutch Sleep Self Report questionnaire: 'Do you fall asleep in about 20 minutes?' (score reversed), 'Do you wake up at night when your parents think you are asleep?' and 'Do you feel sleepy during the day?'.[41] Children or parents indicate the frequency in the past week: rarely (0–1 times), sometimes (2–4 times) and usually (5–7 times). Higher scores indicate more sleep disturbances.

School absence

The cost questionnaire includes an item about school absence in the past 3 months due to abdominal pain/discomfort. Where absence has occurred, they are asked to report the number of days the child actually attended and should have attended.

Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,[42] which includes 35 items on physical symptoms. Scores range from 0 (no problems) to 4 (a lot), and higher scores indicate more somatic complaints. The Dutch version has good psychometric properties.[43]

Cost utility

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost utility calculations.[44] It contains a descriptive questionnaire and a visual analogue scale. The descriptive system covers five dimensions (i.e. mobility, self-care, doing usual activities, pain or discomfort, and emotions). Each dimension is rated on three levels: no problems (1 point), some problems (2 points) and a lot of problems (3 points). Children use a visual analogue scale that ranges from 0 to 100 to rate their overall health (ranging from the worst to the best imaginable health). The EQ-5D-Y is feasible, reliable and valid for children aged 8 years and older.[45] Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

Costs

Parents provide information on both medical and non-medical costs using adapted versions of the iMTA Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ).[46] This covers visits to health care providers, prescribed medication and hospital admissions, and out-of-pocket expenses (e.g. over-the-counter medication, child care, productivity losses and travel costs). In addition, researchers screen the medical records of participating children from 3 months before to 12 months after baseline, seeking to identify the number of GP visits, medication prescriptions, referrals to health care providers, hospital admissions and interventions for FAP.

Evaluation of intervention

Usage of intervention

The website is used to collect usage data and measure adherence in the intervention group. This includes the frequency and duration of intervention use (e.g. when and for how long children log in) plus data on selected exercises (e.g. the exercise chosen and the time listened to). Children are encouraged to attempt the exercises using their own imagination, without listening to the exercises. Given that this is not registered on the website, the follow-up questionnaires include an item about whether children performed the exercises without using the website.

Quality of exercises

At 3 months, children in the intervention group rate the quality of each exercise with an overall score from 0 (bad) to 10 (excellent) and describe what they liked about the exercises and what they think could be improved.

Covariates

The pre-specified covariates are age (<12 vs. ≥12 years), baseline severity of pain/discomfort and treatment expectations. Children and parents are asked to give their expectations of self-hypnosis by rating whether it will improve symptoms on an 11-point scale from 0 (not at all) to 10 (complete recovery). They are also asked whether they have a (strong) preference for CAU alone or home-based guided hypnotherapy plus CAU.[29]

Sample size calculation

We expect adequate relief in 55% of children in the CAU group and 75% of children in the intervention group at 12 months, [3,24] indicating a required difference of 20% to define treatment success. Therefore, a minimum of 90 children per group are necessary to detect treatment success with 80% power at the 5% significance level. Allowing total loss to follow-up of 10%, we aim to include 100 children per group (200 in total).

Statistical analysis

Clinical effectiveness

We will use appropriate descriptive statistics to describe baseline characteristics in both groups.

Estimates of treatment effects (proportions, adjusted mean differences or odds ratios, as appropriate) will be presented with 95% confidence intervals and p-values. All outcomes will first be analysed on an intention-to-treat basis, including all children by the group to which they were randomised. We will then perform per-protocol analyses, including children who did not perform hypnotherapy in the control group and children who listened to at least 80% of one exercise in the intervention group, based on usage data from the website.

The primary outcome will be analysed by logistic multilevel regression modelling, considering relevant covariates. The secondary outcomes will be analysed by logistic (dichotomous variables) and linear (continuous variables) multilevel analyses to investigate the longitudinal relationship between groups. Analysis will be at the patient level for repeated measures in time (baseline, 3, 6 and 12 months), again considering relevant covariates.

Economic evaluation

Costs will be calculated from a societal perspective with a time horizon of 12 months. Health care consumption will be assessed based on current Dutch guidelines for economic evaluation,[47] calculating the cost for use of the intervention website based on the true resources used. We will perform both cost-effectiveness and cost-utility analyses to compare costs and effects between treatment groups. The cost-effectiveness analysis will include the primary outcome, calculating an incremental cost-effectiveness ratio with the added costs or savings expressed per additional patient with adequate symptoms relief. The cost-utility analysis will use the EQ-5D-Y outcome and express the added costs per additional quality-adjusted life year gained. Finally, we will perform bootstrap re-sampling for both cost analyses to produce confidence intervals, and we will plot cost-effectiveness planes and acceptability curves.

Patient and public involvement

We collaborated with the Dutch Child and Hospital Foundation (*Stichting Kind en Ziekenhuis*) and have incorporated their recommendations in the grant proposal, patient information letters

and recruitment strategies. They have also agreed to help disseminate our results to the public. The foundation's Child Advisory Board evaluated the user experience of the website before it was finalised for the study. Additionally, we asked eight children with FAP or IBS about the primary outcome and incorporated their recommendation when setting 'adequate relief' as our primary outcome.

ETHICS AND DISSEMINATION

Ethical approval and consent to participate

The Medical Ethics Review Committee of the University Medical Center Groningen has reviewed and approved the ZelfHy study (METc2020/237). Protocol amendments are communicated to the ethics committee and participating GPs as needed. To meet the requirements of Dutch law for medical research (*Wet Medisch Onderzoek*), participating GPs are asked to agree to study protocol adherence and either parents (age <12 years), parents and the child (age 12–15 years) or the child only (age 16–17 years) are asked to provide written informed consent (Supplement 3).

Dissemination

Newsletters concerning study progress and any interim results are disseminated to participants and participating GPs via the study website and e-mail. The study findings will also be presented at (inter)national conferences and published in peer-reviewed journals, ensuring the dissemination of the results to relevant stakeholders, such as GPs (NHG), paediatricians (Dutch Association for Child Paediatrics) and patients (Child and Hospital Foundation, Dutch Digestive Foundation and thuisarts.nl). Study data will be made available on request.

DISCUSSION

The home-based guided hypnotherapy provided in this trial represents an eHealth intervention,

delivering or enhancing health services and information through the internet and related technologies.[48] Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,[49-52] proving ideal for use in primary care due to the accessibility and low cost of the exercises. A combination of this eHealth strategy with GP communication and education may help empower patients to take control of their own health and learn to manage their symptoms without others.[53,54] This strategy supports current efforts to help children with functional complaints learn to manage, rather than completely remove, pain. Despite the expected suitability of our intervention for children with FAP or IBS in primary care, several potential issues warrant further discussion.

The primary outcome could raise questions because the European Medicines Agency and Food and Drug Administration recommend using an 11-point NRS as the primary outcome when assessing abdominal pain.[55,56] However, these recommendations are based on studies in adults, with no trials measuring whether they also apply to children and a lack of evidence about the optimal treatment outcome in children. Given these issues, we have based our outcomes on recommendations for clinical trials in children with FAP or IBS, which allow the use of an overall measure of change with treatment, a meaningful clinically important difference and a percentage change in symptoms.[33] We selected adequate relief as our primary outcome, corresponding to an overall measure of change with treatment, because treatment in primary care aims to reduce the burden caused by abdominal pain or discomfort (e.g. reducing school absence). Supporting our choice, healthcare professionals, children and parents ranked adequate relief as one of the most important outcome measures.[30]

This trial benefits from using a pragmatic approach characterised by strong applicability and external generalisability to real-world practice. However, this approach not only has low internal validity due to the lack of blinding and potential for sub-optimal adherence but also

precludes etiologic conclusions about the isolated effect of hypnotherapy in primary care.[57,58] To increase our understanding for primary care implementation, we plan to supplement this research with a qualitative evaluation of the acceptability of, and facilitators and barriers related to, home-based guided hypnotherapy.

Recruitment according to our initial protocol was hampered by fewer children than anticipated presenting to GPs with functional abdominal complaints, probably due to a higher threshold to see a GP for non-acute complaints during the covid-19 pandemic. Therefore, we adjusted the recruitment strategy to allow self-referral by children and/or parents. Although this could result in the inclusion of children with less severe complaints, which could in turn influence the primary outcome, we still require that these children visit their GP to optimise comparability. We are keeping track of how patients are recruited to allow later evaluation of differences by the strategy used. Furthermore, we chose to rely on the GP's assessment of FAP or IBS in line with current practice in primary care, which also increases the external validity in terms of generalisability. Studies in specialist paediatric care often include children with FAP or IBS based on the Rome criteria, which may differ from our study population. However, by measuring the Rome criteria at baseline, we can evaluate differences between children with and without FAP or IBS according to this standard.

In summary, this protocol describes our approach to study the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care. In the absence of comparable research in this setting, this study could lead to hypnotherapy being recommended as a supplement to GP-delivered CAU and could improve outcomes for these challenging disorders.

AUTHOR'S CONTRIBUTIONS

GAH, MYB, KMV, MAB and AMV conceived the original research concept. All authors contributed to the study design. ING and ALvdV are responsible for data collection and management during the trial. ING drafted and revised this manuscript. All authors have contributed important intellectual content to the manuscript and have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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FIGURE LEGENDS

Figure 1. Study design

General practitioners screen children for eligibility before randomisation to the control and intervention groups.

SUPPLEMENTAL MATERIAL

Supplement 1. International Classification of Primary Care codes for retrospective search

Supplement 2. Quick reference card for general practitioners

Supplement 3. Informed consent forms

EXCLUSIVE LICENCE

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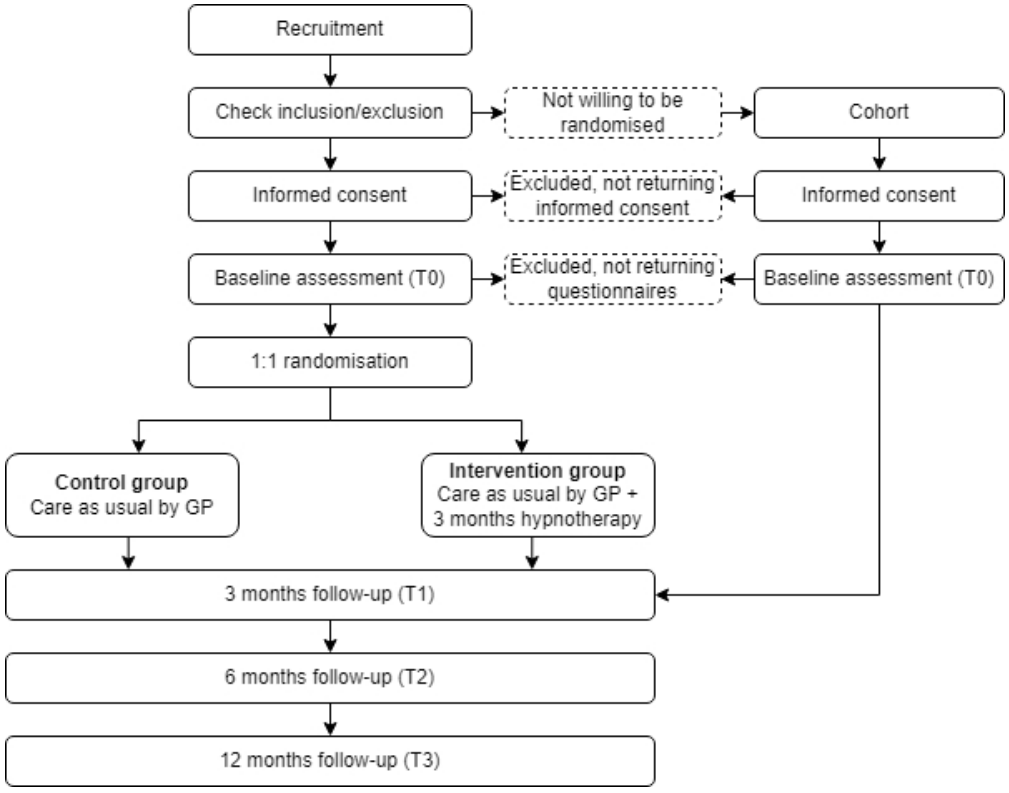

General practitioners screen children for eligibility before randomisation to the control and intervention groups.

212x166mm (72 x 72 DPI)

Supplement 1. International Classification of Primary Care codes for retrospective search

D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D06	Abdominal pain localized other
D11	Diarrhoea
D12	Constipation
D18	Change in faeces/bowel movements
D27	Fear of digestive disease other
D29	Digestive symptom/complaint other
D93	Irritable bowel syndrome
D99	Disease digestive system other

Supplement 2. Quick reference card for general practitioners

REFERENCE CARD OF NHG GUIDELINE HIGHLIGHTS

Definition, epidemiology and diagnostics

Functional abdominal gastrointestinal diseases are '*abdominal pain for which the general practitioner (GP) does not presume underlying tissue damage, somatic causes, or metabolic or anatomic abnormalities based on anamnesis and physical examination*'. The two most important forms are functional abdominal pain and irritable bowel syndrome.

Per norm practice (practice size of 2095 patients) per year, a GP sees on average 10 new children with functional abdominal complaints, more girls than boys. This corresponds with 90% of the children with chronic abdominal pain. Abdominal complaints lasting more than one week increases the chance of functional abdominal pain.

Indication for somatic cause:

- Diarrhoea > 10 days → consider faeces test for parasites
- Indication celiac disease → serologic test or referral to paediatrician
- Indication irritable bowel disease → erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy → pregnancy test

Absence of indication for somatic cause:

- Clinical urine tests to rule out urinary tract infection

Other diagnostics are not recommended.

Rome III criteria in NHG guideline

Functional abdominal pain

1. Recurrent or continue abdominal pain;
2. Abdominal pain ≥ 1 time per week during ≥ 2 months prior to presentation
3. No indication for anatomic, inflammatory, metabolic or neoplastic processes that can explain the abdominal pain

Irritable bowel syndrome

Definition: abdominal pain ≥ 1 time per week during ≥ 2 months, accompanied 1 on 4 times with ≥ 2 of the following:

1. Improvement with defecation
2. Changed defecation frequency
3. Changed stool shape

NHG guideline treatment

Communication – education – reassurance

Education and non-pharmacological treatment:

- Actively involve child and parents/guardians during recovery and policy, adhere to their ideas
- Explain that the gut can oversensitively react to a variety of incentives, that thoughts and feelings can influence the gut and abdomen, and vice versa, abdominal pain influences the emergence of fear and other emotions, and that functional abdominal pain is not a precursor of a dangerous or life-threatening condition.
- Stimulate a balanced diet. Do not recommend extra dietary fibre intake.
- Formulate realistic treatment goals targeting on handling the pain and not on pain disappearance.
- Promote returning to normal activities and regular school attendance.

- Stimulate parents/guardians to pay less attention to the abdominal complaints.
- Choose for complain registration in case of insufficient improvement or recurrent complaints.

Follow-up:

- Follow-up 4 weeks after baseline consultation: discuss the treatment goal and answer questions.
- Advise to return if the character or seriousness of the abdominal pain changes, or if the influence of complaints on activities of daily life increases.

Referral:

- In case of serious persistent functional abdominal pain: discuss additional diagnostics and possible referral with paediatrician.

Hypnotherapy

Medical hypnotherapy is a technique which learns children to gain more control over complaints such as pain and fear, using their own thoughts and fantasies. Research in secondary and tertiary care showed that hypnotherapy by self-exercises helps in 70% of the children.

Supplement 3. Informed consent forms

CONSENT FORM PARTICIPANTS

*For participants aged 12-17 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether I want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my participation. I know I do not have to provide a reason.
- I give consent for retrieving my data from my general practitioner.
- I give consent to collect and use my data for the purpose of this research.
- I give consent for collecting my usage data from the website. This includes the number of logins on the website, and which exercises I listened to.
- I know that some persons can look at my data. These persons are mentioned in the patient information letter. I agree that these persons can look at my data.
- I agree to participate in this research.

- I □ do
  □ do not
  give consent to save my data for a maximum of 15 years and use my data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

First and last name: _____

Signature: _____ Date: __/__/____

*Parents of children aged 12-15 years also have to sign 'Consent form Parents/Guardians'

CONSENT FORM PARENTS/GUARDIANS

*For parents of participants aged 7-15 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

I have been asked to give consent for my child's participation in this medically scientific research.

Name participant (child): _____ Date of birth: __/__/____

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether me and my child want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my child's participation. I know I do not have to provide a reason.
- I know that when my child resists this research, my consent for further participation will expire.
- I give consent for retrieving my child's data from my child's general practitioner as mentioned in the patient information letter.
- I give consent to collect and use my child's data for the purpose of this research.
- I give consent to retrieve my child's usage data from the website. This includes the number of logins on the website, and which exercises my child listened to.
- I know that some persons can look at my child's data. These persons are mentioned in the patient information letter. I agree that these persons can look at my child's data.
- I agree that me and my child participate in this research.

- I □ do
  □ do not
  give consent to save my child's data for a maximum of 15 years and use my child's data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

Parent/guardian 1

First and last name: _____

Signature: _____ Date: __/__/____

Parent/guardian 2

First and last name: _____

Signature: _____ Date: __/__/____

*When the child is younger than 16 years, the parents or guardians sign this form. Children between 12 and 15 years also have to sign 'Consent form Participants'

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8, 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 9, 10, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14, 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14, 15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 16, supplement 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Home-based guided hypnotherapy for children with functional abdominal pain and irritable bowel syndrome in primary care: study protocol for a randomised controlled trial

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Paediatrics
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Home-based guided hypnotherapy for children with functional abdominal pain and irritable bowel syndrome in primary care: study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Children often present to primary care with functional abdominal pain (FAP) or irritable bowel syndrome (IBS), and around half of the children still have abdominal complaints one year later. Hypnotherapy is an evidence-based treatment in specialist care, whereas it lacks evidence in primary care. Therefore, this study will investigate the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care.

Methods and analysis: We report the design of a pragmatic, randomised controlled trial among children aged 7–17 years diagnosed with FAP or IBS by their general practitioner (GP), who will be assessed over 12 months. The control group will receive care as usual by their GP (e.g. communication, education and reassurance), while the intervention group will receive care as usual plus 3 months of home-based guided hypnotherapy via a website. The primary outcome will be the proportion of children with adequate relief from abdominal pain/discomfort at 12 months, analysed on an intention-to-treat basis. Secondary outcomes include adequate pain relief at 3 and 6 months, together with pain/discomfort severity, pain frequency and intensity, daily functioning and impact on function, anxiety and depression, pain beliefs, sleep disturbances, school absence, somatisation, and health care use and costs. We must include 200 children to determine a 20% difference in those with adequate relief (55% control vs. 75% intervention).

Ethics and dissemination: The Medical Ethics Review Committee of the University Medical Center Groningen, the Netherlands, approved this study (METc2020/237). The results will be disseminated to patients, GPs and other stakeholders via e-mail, a dedicated website, peer-reviewed publications and presentations at national and international conferences. We plan to collaborate with the Dutch Society of GPs to implement the results in clinical practice.

Registration details: The Dutch Trial Register: NL8500, and ClinicalTrials.gov: NCT05636358.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Early management of functional abdominal pain (FAP) and irritable bowel syndrome (IBS) through home-based guided hypnotherapy may prevent symptoms becoming chronic.
- Exercises are learnt using digital media (eHealth) and fit well with the target population of young, digitally skilled patients.
- Our pragmatic design has high external generalisability and will provide useful information on the (cost) effectiveness of home-based guided hypnotherapy in a real-world setting.
- The internal validity may be low due to a lack of blinding, with the potential that children in the control group will seek alternative treatment.

ABBREVATIONS

CAU	Care as usual
CSI	Children's Somatisation Inventory
EQ-5D-Y	EuroQol Five Dimensions Health Questionnaire Youth
FAP	Functional Abdominal Pain
GP	General practitioner
IBS	Irritable Bowel Syndrome
iMCQ	iMTA Medical Consumption Questionnaire
iPCQ	iMTA Productivity Cost Questionnaire
NHG	*Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
NRS	Numerical Rating Scale
PBQ	Pain Beliefs Questionnaire
QoL	Quality of Life
RCADS	Revised Anxiety and Depression Scale
REDCap	Research Electronic Data Capture
ZelfHy	*ZelfHypnose*; self-hypnosis

INTRODUCTION

Background and rationale

Children often present to primary care with functional gastrointestinal symptoms, such as functional abdominal pain (FAP) or irritable bowel syndrome (IBS), that cannot be explained by an organic condition and risk becoming chronic.[1-4] These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.[5,6] However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.[7,8] Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,[9] adequate early treatment in primary care could reduce symptoms and the need for secondary care referral.

The general practitioner (GP) functions as a gatekeeper to specialist care in the Netherlands, similar to systems in Canada and the UK.[10] Therefore, all children with FAP or IBS usually present first in primary care, where a GP determines the diagnosis by excluding organic causes through clinical history-taking and physical examination.[11-13] The Dutch Society of GPs (*Nederlands Huisartsen Genootschap;* NHG) guideline for FAP, which recommends good communication, education and reassurance, may not be sufficient for all children.[14,15] Around half of these children still report abdominal complaints after 1 year,[3] underlining the difficulty of treatment.

Children with FAP or IBS often receive psychosocial interventions in specialist paediatric care due to the strong association between functional symptoms and psychological factors (e.g. stress).[12,13,15-17] Hypnotherapy is one such option that involves a therapist inducing a hypnotic state by guiding a patient to respond to suggestions.[18-20] Studies measuring brain responses in adults with IBS show that hypnotherapy may influence gut motility and normalise visceral sensitivity,[21,22] but the mechanisms behind its effect on functional abdominal

symptoms are poorly understood. Hypnotherapy is generally considered safe. Limited trials report side effects or adverse events, but some rare, mild to moderate adverse events have been reported.[23] Indeed, hypnotherapy should always be performed by a trained professional.[24,25] Research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.[18,19,24] Other research in children has proven the non-inferiority of home-based guided hypnotherapy to face-to-face therapist-guided hypnotherapy at 12 months (75% vs. 87% had adequate pain relief, respectively), though with less effectiveness for children who have long-term symptoms.[26] The use of hypnotherapy earlier in the course of symptoms could maximise its benefits, especially if delivered in primary care, but evidence of its (cost) effectiveness is lacking in this setting. Indeed, home-based guided hypnotherapy could improve how GPs manage children with FAP or IBS, potentially leading to a better prognosis, fewer unnecessary referrals and reduced costs.

Hypothesis

We hypothesise that, compared to care as usual (CAU) alone, home-based guided hypnotherapy plus CAU will be more (cost) effective for achieving adequate relief from abdominal pain and discomfort in children with FAP or IBS.

METHODS AND ANALYSIS

Study design

We present the ZelfHy (*ZelfHypnose*; self-hypnosis) study, a pragmatic randomised controlled trial designed to determine the (cost) effectiveness of home-based guided hypnotherapy plus CAU compared to CAU alone for children with FAP or IBS in primary care. Recruitment has already begun, with eligible children being randomised to either the intervention group or the control group and followed for 12 months (Figure 1). This protocol is reported according to the SPIRIT guidelines[27] and the extended CONSORT statement for pragmatic trials.[28]

Study population

The inclusion criteria are as follows: age 7–17 years; attending a GP with chronic gastrointestinal symptoms (e.g. recurrent abdominal pain for ≥2 months or ≥2 episodes in the past 2 months); and GP-diagnosed FAP or IBS. GPs base their diagnosis on the following definition: abdominal pain for which the GP does not presume underlying tissue damage, somatic causes, or metabolic or anatomic abnormalities based on medical history and physical examination.[14] An overview of the Dutch guidelines including definitions of FAP and IBS are shown in Supplement 1. Those with a concomitant organic gastrointestinal disease, abdominal symptoms treated by a paediatrician, mental retardation, psychotic disorders, those who have undergone hypnotherapy in the past year or have poor comprehension of the Dutch language, are excluded. Children who prefer not to randomise can choose to enter a parallel observational cohort study in which they complete the same questionnaires.

Recruitment

We invited GPs through either the Academic General Practitioner Development Network (AHON; *Academisch Huisarts Ontwikkel Netwerk*) or professional connections and asked them to recruit participants. Participating GPs inform eligible children about the trial and provide written information during their consultation. Additionally, GP assistants are performing retrospective searches in GP registration databases each month for potentially eligible children, using a search strategy based on International Classification of Primary Care codes (Supplement 2). Primary care practices in the Netherlands have been recruiting children since November 2020, and we aim to complete recruitment by September 2023. This end date was an adaption from the original end date of September 2022, due to slow inclusion rates.

Slow recruitment by GPs to 1st July 2022 (only 30 children), led us to expand the routes to participation. We now provide information via schools, social media, local media (e.g. newspapers and radio) and different interest groups (e.g. for parents and IBS groups) to allow

self-referral by interested children and/or parents via the study website. The research team then makes contact by telephone, sends the appropriate information and informed consent forms, and asks them to make an appointment with their GP.

Data collection

GPs check the eligibility criteria using specific forms, irrespective of the recruitment method, and send these to the research team. The research team sends the appropriate information and informed consent forms to children recruited via their GP. A researcher then contacts each child by phone to resolve any queries and complete the Rome IV Diagnostic Questionnaire (parent version if <12 years, child version if ≥12 years).[29] The research team only sends the baseline questionnaires after obtaining written informed consent from the participant. After receiving the completed questionnaire, they randomise the participant and inform them of their allocation by phone. Follow-up questionnaires are sent at 3, 6 and 12 months. All questionnaires can be completed in around 30 minutes either on paper or via the REDCap (Research Electronic Data Capture) website.[30] REDCap sends automatic e-mail reminders after 7 and 14 days if the questionnaires are not completed. After 21 days, researchers remind the participants by phone and ask whether the child has experienced adequate relief from abdominal pain/discomfort (primary outcome). Despite the low risk of (severe) adverse events, we have accommodated spontaneous reporting. All study-related and participant information is stored securely at the study site in locked file cabinets that can only be accessed by the researchers.

Randomisation, allocation and blinding

We use a computer-generated 1:1 randomisation list with varying block sizes (4, 6 and 8) that includes stratification by age (<12 years or ≥12 years). An independent methodologist (M.R. de Boer, PhD) manages the randomisation list and treatment allocation. The nature of the intervention precludes blinding of the GPs, children, and parents, but researchers performing the statistical analyses will be blinded to group allocation.

Intervention

Care as usual

All children receive CAU by their GP according to the NHG guideline for abdominal pain in children,[14] offering communication, education and reassurance. The guideline advocates realistic treatment goals that focus on pain management, rather than pain resolution, and follow-up. Since this is a pragmatic trial, we do not restrict GPs in giving any form of treatment because GPs know best what the patient needs. Supplement 1 illustrates an overview of the guideline highlights, which is provided to all participating GPs.

Hypnotherapy by self-exercises

Children in the intervention group are asked to perform home-based guided hypnotherapy for 3 months, supplemented with CAU by their GP. Prior to starting the exercises, a researcher arranges an online video call with the child and parent(s) to explain hypnotherapy, how it can help reduce abdominal pain and how they can access the exercises. Additionally, the child and parent(s) are instructed not to discuss the pain anymore.[31]

We use an existing home-based guided hypnotherapy programme, as described elsewhere,[31] adjusted for this study. This comprises one breathing and progressive relaxation exercise and four visualisation exercises: 'the favourite place', 'the rainbow planet' or 'air balloon' (depending on age version), 'the beach without worries', and 'the slide'. Exercises have been recorded by a hypnotherapist in a digital audio format (MP3). In Table 1, examples of hypnotic suggestions are displayed. The language is adapted to the child's age, with one version each for children aged <12 years and ≥12 years. The intensity, i.e. duration of each exercise is equal for both versions, and feasible for all age groups.[31,32] We include the instructions and exercises for both versions in a newly designed, responsive, login-protected website. Instructions are directly visible on the home page and vary each week. For example,

in the first two weeks, children are instructed to listen to the first two exercises. Every week or every two weeks, a new exercise is introduced. Children can choose which exercise they want to listen to, and they can repeat the exercise for as many times as preferred. Children are asked to listen to the exercises at least five times per week, for 15–20 minutes per day, over 3 months. To improve compliance, they receive automatic e-mail reminders from the website after 14 and 28 days of inactivity.

Table 1. Examples of hypnotic suggestions

Aim	Examples of hypnotic suggestions
Normalising gut functions	"Every day, by practicing your deep breathing, slowly in and out, your belly will feel more and more relaxed."
Ego strengthening	"You can notice that you can keep this nice feeling of confidence with you, for as long as you want, and that you can use this whenever you want to help yourself."
Relaxation	"Pull your shoulders backwards, and hold on, feel the tension, and with a deep sigh, pfffff, you let it go completely. And you can feel how nice it can be to let go of all this stress and fuss, and how good this feels for your belly."

Outcomes

Table 2 gives an overview of the outcome measures and covariates used in this study. The outcomes are based on a recommended set of variables for clinical trials of paediatric FAP disorders.[33] Demographic data are obtained from the inclusion form and outcomes are measured at baseline and at 3, 6 and 12 months' follow-up (T0, T1, T2 and T3, respectively). Parents complete the questionnaires for children aged <12 years, while children aged ≥12 years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

Table 2. Overview of outcome parameters and covariates

Primary outcome	**Source**	**T0**	**T1**	**T2**	**T3**
Adequate pain relief at 12 months	Binary yes/no question				x
Secondary outcomes					
Adequate pain relief at 3 and 6 months	Binary yes/no question		x	x	
Severity of pain/discomfort	NRS-11	x	x	x	x
Pain frequency and intensity	Abdominal pain diary	x	x	x	x
Daily functioning and impact	KIDSCREEN-52	x	x	x	x
Anxiety and depression	RCADS-25	x	x	x	x
Pain beliefs	PBQ	x	x	x	x
Sleep disturbances	Sleep Self Report	x	x	x	x
School absence	Study questionnaire**	x	x	x	x
Somatisation	CSI	x	x	x	x
Utility	EQ-5D-Y	x	x	x	x
Costs	Adjusted iPCQ & iMCQ Medical records	x	x	x	x
Evaluation of intervention					
Usage of intervention*	Study questionnaire**		x	x	x
Quality of exercises*	Study questionnaire**		x		
Covariates					
Age	Study inclusion form	x			
Severity of pain/discomfort	NRS-11	x			
Treatment expectations	Study questionnaire**	x			

*Only for intervention group.

**The study questionnaires were created specifically for this research.

Abbreviations: NRS-11, Numerical Rating Scale-11; RCADS-25, Revised Anxiety and Depression Scale-25; PBQ, Pain Beliefs Questionnaire; CSI, Children's Somatisation Inventory; EQ-5D-Y, EuroQol Five Dimensions Health Questionnaire Youth; iPCQ, iMTA Productivity Cost Questionnaire; iMCQ, iMTA Medical Consumption Questionnaire.

Primary outcome

The primary outcome is the proportion of children with adequate relief of abdominal pain/discomfort after 12 months. The child or parent(s) are asked whether relief from abdominal pain or discomfort has been adequate during the past week, compared to baseline, on a

dichotomous scale (yes/no). Self-reported adequate relief is a well validated outcome measurement in other trials of IBS treatment.[34]

Secondary outcomes

Adequate pain relief at 3 and 6 months

The proportion of children with adequate relief of abdominal pain/discomfort at 3 and 6 months will be assessed using the same dichotomous scale as the primary outcome.

Severity of pain/discomfort

The severity of abdominal pain and/or discomfort in the past week is assessed using a 11-point numerical rating scale (NRS-11) from 0 (no pain) to 10 (worst pain). This scale provides valid and reliable scores in children and adolescents with chronic pain.[35,36]

Pain intensity and frequency

Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,[36] as recommended and often used in other trials of childhood FAP or IBS.[31,36] Pain intensity is assessed using an affective facial pain scale,[37,38] where the faces range from showing no pain at all (score 0) to the most severe pain (score 3). Pain frequency is assessed by asking how long the pain lasted per day, ranging from no pain (score 0) to >2 hours (score 3). The frequency and intensity scores are then totalled for 7 days, giving total ranges of 0–21 per score.[26]

Quality of life

The KIDSCREEN-52 is a reliable and valid health-related QoL questionnaire that measures the impact of abdominal pain on daily functioning and QoL.[39-41] It comprises 52 items covering ten dimensions: physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, relations with parents and home life, social support and peers, school environment, social acceptance (bullying) and financial resources. Participants rate behaviour frequency or attitude intensity in the past week on 5-point Likert scales. Higher scores

correspond to better health-related QoL and well-being.

Anxiety and depression

Symptoms of anxiety and depression are assessed by a short version of the Revised Child Anxiety and Depression Scale (RCADS-25), which is a valid and reliable instrument in Dutch populations.[42] The child or parent indicates how often each of the 20 anxiety and 5 depression items applies to the child on 4-point scales from 0 (never) to 3 (always). Higher scores indicate more symptoms of anxiety and/or depression.

Pain beliefs

The paediatric Pain Beliefs Questionnaire (PBQ) includes 32 items that assess beliefs about abdominal pain.[43] Each item consists of a pain belief statement with responses that range from not true at all (score 0) to very true (score 4). The PBQ comprises three subscales: pain threat (20 items), problem-focused coping efficacy (6 items) and emotion-focused coping efficacy (6 items). A higher score on the pain threat scale indicates a stronger belief that their abdominal pain is a threat. Higher scores on both coping subscales indicate stronger beliefs in their ability to cope with pain using either problem-focused or emotion-focused strategies.

Sleep disturbances

Sleep disturbances are measured using three items from the Dutch Sleep Self Report questionnaire: 'Do you fall asleep in about 20 minutes?' (score reversed), 'Do you wake up at night when your parents think you are asleep?' and 'Do you feel sleepy during the day?'.[44] Children or parents indicate the frequency in the past week: rarely (0–1 times), sometimes (2–4 times) and usually (5–7 times). Higher scores indicate more sleep disturbances.

School absence

The cost questionnaire includes an item about school absence in the past 3 months due to abdominal pain/discomfort. Where absence has occurred, they are asked to report the number of days the child actually attended and should have attended.

Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,[45] which includes 35 items on physical symptoms. Scores range from 0 (no problems) to 4 (a lot), and higher scores indicate more somatic complaints. The Dutch version has good psychometric properties.[46]

Cost utility

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost utility calculations.[47] It contains a descriptive questionnaire and a visual analogue scale. The descriptive system covers five dimensions (i.e. mobility, self-care, doing usual activities, pain or discomfort, and emotions). Each dimension is rated on three levels: no problems (1 point), some problems (2 points) and a lot of problems (3 points). Children use a visual analogue scale that ranges from 0 to 100 to rate their overall health (ranging from the worst to the best imaginable health). The EQ-5D-Y is feasible, reliable and valid for children aged 8 years and older.[48] Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

Costs

Parents provide information on both medical and non-medical costs using adapted versions of the iMTA Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ).[49] This covers visits to health care providers, prescribed medication and hospital admissions, and out-of-pocket expenses (e.g. over-the-counter medication, child care, productivity losses and travel costs). In addition, researchers screen the medical records of participating children from 3 months before to 12 months after baseline, seeking to identify the number of GP visits, medication prescriptions, referrals to health care providers, hospital admissions and interventions for FAP.

Evaluation of intervention

Usage of intervention

The website is used to collect usage data and measure adherence in the intervention group. This includes the frequency and duration of intervention use (e.g. when and for how long children log in) plus data on selected exercises (e.g. the exercise chosen and the time listened to). Children are encouraged to attempt the exercises using their own imagination, without listening to the exercises. And children with technical knowledge might listen to the exercises in another way, e.g. via a download. Given that this is not registered on the website, the follow-up questionnaires include an item about whether and how often children performed the exercises without using the website.

Quality of exercises

At 3 months, children in the intervention group rate the quality of each exercise with an overall score from 0 (bad) to 10 (excellent) and describe what they liked about the exercises and what they think could be improved.

Covariates

The pre-specified covariates are age (<12 vs. ≥12 years), baseline severity of pain/discomfort and treatment expectations. Children and parents are asked to give their expectations of self-hypnosis by rating whether it will improve symptoms on an 11-point scale from 0 (not at all) to 10 (complete recovery). They are also asked whether they have a (strong) preference for CAU alone or home-based guided hypnotherapy plus CAU.[31]

Sample size calculation

We expect adequate relief in 55% of children in the CAU group and 75% of children in the intervention group at 12 months, [3,26] indicating a required difference of 20% to define treatment success. Therefore, a minimum of 90 children per group are necessary to detect treatment success with 80% power at the 5% significance level. Allowing total loss to follow-up of 10%, we aim to include 100 children per group (200 in total).

Statistical analysis

Clinical effectiveness

We will use appropriate descriptive statistics to describe baseline characteristics in both groups. Estimates of treatment effects (proportions, adjusted mean differences or odds ratios, as appropriate) will be presented with 95% confidence intervals and p-values. All outcomes will first be analysed on an intention-to-treat basis, including all children by the group to which they were randomised. We will then perform per-protocol analyses, including children who did not perform hypnotherapy in the control group and children who started at least 4 out of 5 exercises in the intervention group, based on usage data from the website.

The primary outcome will be analysed by logistic multilevel regression modelling, considering relevant covariates. The secondary outcomes will be analysed by logistic (dichotomous variables) and linear (continuous variables) multilevel analyses to investigate the longitudinal relationship between groups. Analysis will be at the patient level for repeated measures in time (baseline, 3, 6 and 12 months), again considering relevant covariates.

Economic evaluation

Costs will be calculated from a societal perspective with a time horizon of 12 months. Health care consumption will be assessed based on current Dutch guidelines for economic evaluation,[50] calculating the cost for use of the intervention website based on the true resources used. We will perform both cost-effectiveness and cost-utility analyses to compare costs and effects between treatment groups. The cost-effectiveness analysis will include the primary outcome, calculating an incremental cost-effectiveness ratio with the added costs or savings expressed per additional patient with adequate symptoms relief. The cost-utility analysis will use the EQ-5D-Y outcome and express the added costs per additional quality-adjusted life year gained. Finally, we will perform bootstrap re-sampling for both cost analyses to produce confidence intervals, and we will plot cost-effectiveness planes and acceptability curves.

Patient and public involvement

We collaborated with the Dutch Child and Hospital Foundation (*Stichting Kind en Ziekenhuis*) and have incorporated their recommendations in the grant proposal, patient information letters and recruitment strategies. They have also agreed to help disseminate our results to the public. The foundation's Child Advisory Board evaluated the user experience of the website before it was finalised for the study. Additionally, we asked eight children with FAP or IBS about the primary outcome and incorporated their recommendation when setting 'adequate relief' as our primary outcome.

ETHICS AND DISSEMINATION

Ethical approval and consent to participate

The Medical Ethics Review Committee of the University Medical Center Groningen has reviewed and approved the ZelfHy study (METc2020/237). Protocol amendments are communicated to the ethics committee and participating GPs as needed. To meet the requirements of Dutch law for medical research (*Wet Medisch Onderzoek*), participating GPs are asked to agree to study protocol adherence and either parents (age <12 years), parents and the child (age 12–15 years) or the child only (age 16–17 years) are asked to provide written informed consent (Supplement 3).

Dissemination

Newsletters concerning study progress and any interim results are disseminated to participants and participating GPs via the study website and e-mail. The study findings will also be presented at (inter)national conferences and published in peer-reviewed journals, ensuring the dissemination of the results to relevant stakeholders, such as GPs (NHG), paediatricians (Dutch Association for Child Paediatrics) and patients (Child and Hospital Foundation, Dutch Digestive Foundation and thuisarts.nl). Study data will be made available on request.

DISCUSSION

The home-based guided hypnotherapy provided in this trial represents an eHealth intervention, delivering or enhancing health services and information through the internet and related technologies.[51] Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,[52-55] proving ideal for use in primary care due to the accessibility and low cost of the exercises. Most adult IBS patients prefer remote hypnotherapy over face-to-face hypnotherapy, although this has not been studied in children and adolescents.[56] A combination of this eHealth strategy with GP communication and education may help empower patients to take control of their own health and learn to manage their symptoms without others.[57,58] This strategy supports current efforts to help children with functional complaints learn to manage, rather than completely remove, pain. Despite the expected suitability of our intervention for children with FAP or IBS in primary care, several potential issues warrant further discussion.

The primary outcome could raise questions because the European Medicines Agency and Food and Drug Administration recommend using an 11-point NRS as the primary outcome when assessing abdominal pain.[59,60] However, these recommendations are based on studies in adults, with no studies measuring validity and whether they also apply to children, there is a lack of evidence about the optimal treatment outcome in children. Given these issues, we have based our outcomes on recommendations for clinical trials in children with FAP or IBS, which allow the use of an overall measure of change with treatment, a meaningful clinically important difference and a percentage change in symptoms.[36] We selected adequate relief as our primary outcome, corresponding to an overall measure of change with treatment, because treatment in primary care aims to reduce the burden caused by abdominal pain or discomfort (e.g. reducing school absence). The aim of hypnotherapy is not only to reduce abdominal pain, but also to reduce discomfort. We believe that adequate relief of pain/discomfort measures this best. Supporting our choice, healthcare professionals, children and parents ranked adequate relief as

one of the most important outcome measures.[33]

This trial benefits from using a pragmatic approach characterised by strong applicability and external generalisability to real-world practice. However, this approach not only has low internal validity due to the lack of blinding and potential for sub-optimal adherence but also precludes etiologic conclusions about the isolated effect of hypnotherapy in primary care.[61,62] To increase our understanding for primary care implementation, we plan to supplement this research with a qualitative evaluation of the acceptability of, and facilitators and barriers related to, home-based guided hypnotherapy.

Recruitment according to our initial protocol was hampered by fewer children than anticipated presenting to GPs with functional abdominal complaints, probably due to a higher threshold to see a GP for non-acute complaints during the covid-19 pandemic. Therefore, we adjusted the recruitment strategy to allow self-referral by children and/or parents. Although this could result in the inclusion of children with less severe complaints, which could in turn influence the primary outcome, we still require that these children visit their GP to optimise comparability. We are keeping track of how patients are recruited to allow later evaluation of differences by the strategy used. Furthermore, we chose to rely on the GP's assessment of FAP or IBS in line with current practice in primary care, which also increases the external validity in terms of generalisability. Studies in specialist paediatric care often include children with FAP or IBS based on the Rome criteria, which may differ from our study population. However, by measuring the Rome criteria at baseline, we can evaluate differences between children with and without FAP or IBS according to this standard.

In summary, this protocol describes our approach to study the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care. In the absence of comparable research in this setting, this study could lead to hypnotherapy being recommended as a supplement to GP-delivered CAU and could improve outcomes for these

challenging disorders.

AUTHOR'S CONTRIBUTIONS

GAH, MYB, KMV, MAB and AMV conceived the original research concept. ING, TF, HJM-A, AH, ALvdV, KMV, MAB, AMV, MYB and GAH contributed to the study design. ING and ALvdV are responsible for data collection and management during the trial. ING drafted and revised this manuscript. All authors have contributed important intellectual content to the manuscript and have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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REGISTRATION STATEMENT

This study was initially registered in the Dutch Trial Register prior to enrollment of the first participant. Since this register was no longer functional, we additionally registered our study in the ClinicalTrials.gov registry.

EXCLUSIVE LICENCE

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FIGURE LEGENDS

Figure 1. Study design

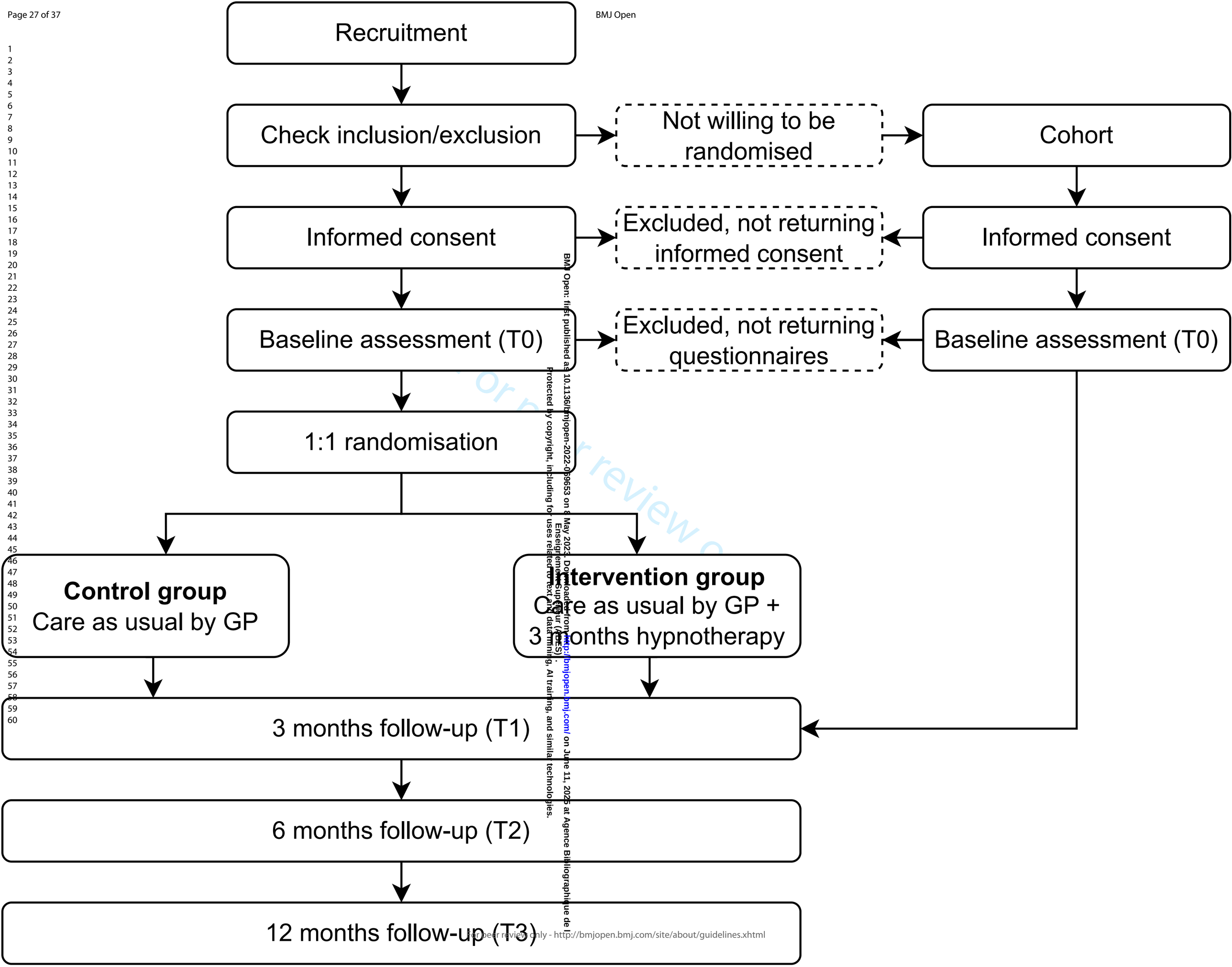
General practitioners screen children for eligibility before randomisation to the control and intervention groups.

SUPPLEMENTAL MATERIAL

Supplement 1. Quick reference card for general practitioners

Supplement 2. International Classification of Primary Care codes for retrospective search

Supplement 3. Informed consent forms



Supplement 1. Quick reference card for general practitioners

REFERENCE CARD OF NHG GUIDELINE HIGHLIGHTS

Definition, epidemiology and diagnostics

Functional abdominal gastrointestinal diseases are '*abdominal pain for which the general practitioner (GP) does not presume underlying tissue damage, somatic causes, or metabolic or anatomic abnormalities based on anamnesis and physical examination*'. The two most important forms are functional abdominal pain and irritable bowel syndrome.

Per norm practice (practice size of 2095 patients) per year, a GP sees on average 10 new children with functional abdominal complaints, more girls than boys. This corresponds with 90% of the children with chronic abdominal pain. Abdominal complaints lasting more than one week increases the chance of functional abdominal pain.

Indication for somatic cause:

- Diarrhoea > 10 days → consider faeces test for parasites
- Indication celiac disease → serologic test or referral to paediatrician
- Indication irritable bowel disease → erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy → pregnancy test

Absence of indication for somatic cause:

- Clinical urine tests to rule out urinary tract infection

Other diagnostics are not recommended.

Rome III criteria in NHG guideline

Functional abdominal pain

1. Recurrent or continue abdominal pain;
2. Abdominal pain ≥ 1 time per week during ≥ 2 months prior to presentation
3. No indication for anatomic, inflammatory, metabolic or neoplastic processes that can explain the abdominal pain

Irritable bowel syndrome

Definition: abdominal pain ≥ 1 time per week during ≥ 2 months, accompanied 1 on 4 times with ≥ 2 of the following:

1. Improvement with defecation
2. Changed defecation frequency
3. Changed stool shape

NHG guideline treatment

Communication – education – reassurance

Education and non-pharmacological treatment:

- Actively involve child and parents/guardians during recovery and policy, adhere to their ideas
- Explain that the gut can oversensitively react to a variety of incentives, that thoughts and feelings can influence the gut and abdomen, and vice versa, abdominal pain influences the emergence of fear and other emotions, and that functional abdominal pain is not a precursor of a dangerous or life-threatening condition.
- Stimulate a balanced diet. Do not recommend extra dietary fibre intake.
- Formulate realistic treatment goals targeting on handling the pain and not on pain disappearance.
- Promote returning to normal activities and regular school attendance.

- Stimulate parents/guardians to pay less attention to the abdominal complaints.
- Choose for complain registration in case of insufficient improvement or recurrent complaints.

Follow-up:

- Follow-up 4 weeks after baseline consultation: discuss the treatment goal and answer questions.
- Advise to return if the character or seriousness of the abdominal pain changes, or if the influence of complaints on activities of daily life increases.

Referral:

- In case of serious persistent functional abdominal pain: discuss additional diagnostics and possible referral with paediatrician.

Hypnotherapy

Medical hypnotherapy is a technique which learns children to gain more control over complaints such as pain and fear, using their own thoughts and fantasies. Research in secondary and tertiary care showed that hypnotherapy by self-exercises helps in 70% of the children.

Supplement 2. International Classification of Primary Care codes for retrospective search

D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D06	Abdominal pain localized other
D11	Diarrhoea
D12	Constipation
D18	Change in faeces/bowel movements
D27	Fear of digestive disease other
D29	Digestive symptom/complaint other
D93	Irritable bowel syndrome
D99	Disease digestive system other

Supplement 3. Informed consent forms

CONSENT FORM PARTICIPANTS

*For participants aged 12-17 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether I want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my participation. I know I do not have to provide a reason.
- I give consent for retrieving my data from my general practitioner.
- I give consent to collect and use my data for the purpose of this research.
- I give consent for collecting my usage data from the website. This includes the number of logins on the website, and which exercises I listened to.
- I know that some persons can look at my data. These persons are mentioned in the patient information letter. I agree that these persons can look at my data.
- I agree to participate in this research.

- I □ do
  □ do not
  give consent to save my data for a maximum of 15 years and use my data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

First and last name: _____

Signature: _____ Date: __/__/____

*Parents of children aged 12-15 years also have to sign 'Consent form Parents/Guardians'

CONSENT FORM PARENTS/GUARDIANS

*For parents of participants aged 7-15 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

I have been asked to give consent for my child's participation in this medically scientific research.

Name participant (child): _____ Date of birth: __/__/____

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether me and my child want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my child's participation. I know I do not have to provide a reason.
- I know that when my child resists this research, my consent for further participation will expire.
- I give consent for retrieving my child's data from my child's general practitioner as mentioned in the patient information letter.
- I give consent to collect and use my child's data for the purpose of this research.
- I give consent to retrieve my child's usage data from the website. This includes the number of logins on the website, and which exercises my child listened to.
- I know that some persons can look at my child's data. These persons are mentioned in the patient information letter. I agree that these persons can look at my child's data.
- I agree that me and my child participate in this research.

- I □ do
  □ do not
  give consent to save my child's data for a maximum of 15 years and use my child's data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

Parent/guardian 1

First and last name: _____

Signature: _____ Date: __/__/____

Parent/guardian 2

First and last name: _____

Signature: _____ Date: __/__/____

*When the child is younger than 16 years, the parents or guardians sign this form. Children between 12 and 15 years also have to sign 'Consent form Participants'

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8, 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 9, 10, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14, 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14, 15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 16, supplement 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Home-based guided hypnotherapy for children with functional abdominal pain and irritable bowel syndrome in primary care: study protocol for a randomised controlled trial

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Home-based guided hypnotherapy for children with functional abdominal pain and irritable bowel syndrome in primary care: study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Children often present to primary care with functional abdominal pain (FAP) or irritable bowel syndrome (IBS), and around half still have abdominal complaints one year later. Hypnotherapy is an evidence-based treatment that is used in specialist care, but it lacks evidence in primary care. This study will investigate the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care.

Methods and analysis: We report the design of a pragmatic randomised controlled trial among children aged 7–17 years, diagnosed with FAP or IBS by their general practitioner (GP), with assessments over 12 months. The control group will receive care as usual by their GP (e.g. communication, education and reassurance), while the intervention group will receive care as usual plus 3 months of home-based guided hypnotherapy via a website. The primary outcome will be the proportion of children with adequate relief from abdominal pain/discomfort at 12 months, analysed on an intention-to-treat basis. Secondary outcomes will include the adequacy of pain relief at 3 and 6 months, pain/discomfort severity, pain frequency and intensity, daily functioning and impact on function, anxiety and depression, pain beliefs, sleep disturbances, school absence, somatisation, and health care use and costs. We must include 200 children to determine a 20% difference in those with adequate relief (55% control vs. 75% intervention).

Ethics and dissemination: The Medical Ethics Review Committee of the University Medical Center Groningen, the Netherlands, approved this study (METc2020/237). The results will be disseminated to patients, GPs and other stakeholders via e-mail, a dedicated website, peer-reviewed publications and presentations at national and international conferences. We plan to collaborate with the Dutch Society of GPs to implement the results in clinical practice.

Registration details: The Dutch Trial Register: NL8500, and ClinicalTrials.gov: NCT05636358.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Early management of functional abdominal pain (FAP) and irritable bowel syndrome (IBS) through home-based guided hypnotherapy may prevent symptoms becoming chronic.
- Exercises are learnt using digital media (eHealth) and fit well with the target population of young, digitally skilled patients.
- Our pragmatic design has high external generalisability and will provide useful information on the (cost) effectiveness of home-based guided hypnotherapy in a real-world setting.
- The internal validity may be low due to a lack of blinding, with the potential that children in the control group will seek alternative treatment.

ABBREVATIONS

CAU	Care as usual
CSI	Children's Somatisation Inventory
EQ-5D-Y	EuroQol Five Dimensions Health Questionnaire Youth
FAP	Functional Abdominal Pain
GP	General practitioner
IBS	Irritable Bowel Syndrome
iMCQ	iMTA Medical Consumption Questionnaire
iPCQ	iMTA Productivity Cost Questionnaire
NHG	*Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
NRS	Numerical Rating Scale
PBQ	Pain Beliefs Questionnaire
QoL	Quality of Life
RCADS	Revised Anxiety and Depression Scale
REDCap	Research Electronic Data Capture
ZelfHy	*ZelfHypnose*; self-hypnosis

INTRODUCTION

Background and rationale

Children often present to primary care with functional gastrointestinal symptoms, such as functional abdominal pain (FAP) or irritable bowel syndrome (IBS), that cannot be explained by an organic condition and risk becoming chronic.[1-4] These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.[5,6] However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.[7,8] Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,[9] adequate early treatment in primary care could reduce symptoms and the need for referral.

The general practitioner (GP) functions as a gatekeeper to specialist care in the Netherlands, similar to systems in Canada and the UK.[10] Therefore, children with FAP or IBS usually present first in primary care, where a GP determines the diagnosis by excluding organic causes based on clinical history and physical examination.[11-13] The guideline for FAP published by the Dutch Society of GPs (*Nederlands Huisartsen Genootschap;* NHG), which recommends good communication, education and reassurance, may not be sufficient for all children.[14,15] Around half of these children still report abdominal complaints after 1 year,[3] underlining the difficulty of treatment.

Children with FAP or IBS may receive psychosocial interventions in specialist paediatric care due to the strong association between functional symptoms and psychological factors (e.g. stress).[12,13,15-17] Hypnotherapy is one such option that involves a therapist inducing a hypnotic state by guiding a patient to respond to suggestions.[18-20] Studies measuring brain responses in adults with IBS show that hypnotherapy may influence gut motility and normalise visceral sensitivity,[21,22] though the mechanisms behind its effect on functional abdominal

symptoms are poorly understood. Hypnotherapy is generally considered safe. Limited trials report side effects or adverse events, but some rare, mild to moderate adverse events have been reported.[23] Indeed, hypnotherapy should always be performed by a trained professional.[24,25] Research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.[18,19,24] Other research in children has proven the non-inferiority of home-based guided hypnotherapy compared to face-to-face therapist-guided hypnotherapy at 12 months (adequate pain relief in 75% and 87%, respectively), though with lower effectiveness among children with long-term symptoms.[26] The earlier use of hypnotherapy could maximise its benefits, especially if delivered in primary care. Indeed, home-based guided hypnotherapy could improve how GPs manage children with FAP or IBS, potentially leading to a better prognosis, fewer unnecessary referrals and reduced costs. However, evidence of its (cost) effectiveness in primary care is lacking.

Hypothesis

We hypothesise that, compared to care as usual (CAU) alone, home-based guided hypnotherapy plus CAU will be more (cost) effective for achieving adequate relief from abdominal pain and discomfort in children with FAP or IBS.

METHODS AND ANALYSIS

Study design

We present the ZelfHy (*ZelfHypnose*; self-hypnosis) study, a pragmatic randomised controlled trial designed to determine the (cost) effectiveness of home-based guided hypnotherapy plus CAU compared to CAU alone for children with FAP or IBS in primary care. Recruitment has already begun, with eligible children being randomised to either the intervention group or the control group and followed for 12 months (Figure 1). This protocol is reported according to the SPIRIT guidelines[27] and the extended CONSORT statement for pragmatic trials.[28]

Study population

The inclusion criteria are as follows: age 7–17 years; attending a GP with chronic gastrointestinal symptoms (e.g. recurrent abdominal pain for ≥2 months or ≥2 episodes in the past 2 months); and GP-diagnosed FAP or IBS. GPs base their diagnosis on the following definition: abdominal pain for which the GP does not presume underlying tissue damage, somatic causes, or metabolic or anatomic abnormalities based on medical history and physical examination.[14] An overview of the Dutch guidelines including definitions of FAP and IBS are shown in Supplement 1. Those with a concomitant organic gastrointestinal disease, abdominal symptoms treated by a paediatrician, intellectual disability, psychotic disorders, a history of hypnotherapy in the past year, or poor comprehension of the Dutch language are excluded. Children who prefer not to randomise can choose to enter a parallel observational cohort study in which they complete the same questionnaires.

Recruitment

We invited GPs either from the Academic General Practitioner Development Network (AHON; *Academisch Huisarts Ontwikkel Netwerk*) or through professional connections. Participating GPs are then asked to recruit study participants during consultations by informing eligible children about the trial and providing written information. Additionally, GP assistants are performing retrospective searches in GP registration databases each month for potentially eligible children, using a search strategy based on International Classification of Primary Care codes (Supplement 2). Primary care practices in the Netherlands have been recruiting children since November 2020, and although we had aimed to complete recruitment by September 2022, slow recruitment has necessitated that we extend the end date to September 2023. This slow recruitment by GPs before 1st July 2022 (only 30 children) also led us to expand the routes to participation. Since then, we have now provided information via schools, social media, local media (e.g. newspapers and radio) and different interest groups (e.g. for parents and IBS groups)

to allow self-referral by interested children and/or parents via the study website. The research team then makes contact by telephone, sends the appropriate information and informed consent forms, and asks them to make an appointment with their GP.

Data collection

GPs check the study eligibility criteria using specific forms, irrespective of the recruitment method, and send these to the research team. The research team sends the appropriate information and consent forms to children recruited via their GP. A researcher then contacts each child by phone to resolve queries and complete the Rome IV Diagnostic Questionnaire (parent version if <12 years, child version if ≥12 years).[29] The research team only sends the baseline questionnaires after obtaining written informed consent from the participant. After receiving the completed questionnaire, they randomise the participant and inform them of their allocation by phone. Follow-up questionnaires are sent at 3, 6 and 12 months. All questionnaires can be completed in around 30 minutes on paper or via the REDCap (Research Electronic Data Capture) website.[30] REDCap sends automatic e-mail reminders after 7 and 14 days if the questionnaires are not completed. After 21 days, researchers remind the participants by phone and ask whether the child has experienced adequate relief from abdominal pain/discomfort (primary outcome). Despite the low risk of (severe) adverse events, we have accommodated spontaneous reporting. All study-related and participant information is stored securely at the study site in locked file cabinets that can only be accessed by researchers.

Randomisation, allocation and blinding

We use a computer-generated 1:1 randomisation list with varying block sizes (4, 6 and 8) and stratification by age (<12 years or ≥12 years). An independent methodologist (M.R. de Boer, PhD) manages the randomisation list and treatment allocation. The nature of the intervention precludes blinding of the GPs, children, and parents, but researchers performing the statistical analyses will be blinded to group allocation.

Intervention

Care as usual

All children receive GP-based CAU according to the NHG guideline for abdominal pain in children,[14] which includes communication, education and reassurance. The guideline advocates realistic treatment goals that focus on pain management, rather than pain resolution, and appropriate follow-up. Since this is a pragmatic trial, we have not restricted the treatments offered by GPs. Supplement 1 provides an overview of the guideline, which is provided to all participating GPs.

Hypnotherapy by self-exercises

Children in the intervention group receive CAU and are asked to perform home-based guided hypnotherapy for 3 months. Before starting the exercises, a researcher arranges an online video call with the child and parent(s) to explain hypnotherapy, how it can help reduce abdominal pain and how they can access the exercises. Additionally, the child and parent(s) are instructed not to discuss the pain anymore.[31]

We use an existing home-based guided hypnotherapy programme, as described elsewhere,[31] with adjustments. The programme comprises one breathing and progressive relaxation exercise and four visualisation exercises: 'the favourite place', 'the rainbow planet' or 'air balloon' (depending on age), 'the beach without worries', and 'the slide'. Exercises have been recorded by a hypnotherapist in a digital audio format (MP3). Table 1 provides examples of the hypnotic suggestions. The language is adapted to the child's age, with one version each for children aged <12 years and ≥12 years. Both versions are of equal intensity (e.g., exercise duration) and are feasible for all relevant age groups.[31,32] We include the instructions and exercises for both versions in a newly designed, responsive, login-protected website. Instructions are directly visible on the home page and vary each week. For example, children

are instructed to listen to the first two exercises for the first two weeks, with a new exercise introduced every week or two weeks. Children can choose what exercise they follow and can repeat it as many times as they want. However, they are asked to listen to the exercises at least five times per week, for 15–20 minutes per day, over 3 months. To improve compliance, they receive automatic e-mail reminders from the website after 14 and 28 days of inactivity.

Table 1. Examples of hypnotic suggestions

Aim	Examples of hypnotic suggestions
Normalising gut functions	*"Every day, by practicing your deep breathing, slowly in and out, your belly will feel more and more relaxed".*
Ego strengthening	*"You can notice that you can keep this nice feeling of confidence with you, for as long as you want, and that you can use this whenever you want to help yourself".*
Relaxation	*"Pull your shoulders backwards and hold on, feel the tension, and with a deep sigh,* [hypnotherapist makes the sound of a relaxing sigh] *you let go completely. And you can feel how nice it can be to let go of all this stress and fuss, and how good this feels for your belly".*

Outcomes

Table 2 gives an overview of the outcome measures and covariates used in this study. The outcomes are based on a recommended set of variables for clinical trials of paediatric FAP disorders.[33] Demographic data are obtained from the inclusion form, and outcomes are measured at baseline and at 3, 6 and 12 months' follow-up (T0, T1, T2 and T3, respectively). Parents complete the questionnaires for children aged <12 years, while children aged ≥12 years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

Table 2. Overview of outcome parameters and covariates

Primary outcome	**Source**	**T0**	**T1**	**T2**	**T3**
Adequate pain relief at 12 months	Binary yes/no question				x
Secondary outcomes					
Adequate pain relief at 3 and 6 months	Binary yes/no question		x	x	
Severity of pain/discomfort	NRS-11	x	x	x	x
Pain frequency and intensity	Abdominal pain diary	x	x	x	x
Daily functioning and impact	KIDSCREEN-52	x	x	x	x
Anxiety and depression	RCADS-25	x	x	x	x
Pain beliefs	PBQ	x	x	x	x
Sleep disturbances	Sleep Self Report	x	x	x	x
School absence	Study questionnaire**	x	x	x	x
Somatisation	CSI	x	x	x	x
Utility	EQ-5D-Y	x	x	x	x
Costs	Adjusted iPCQ & iMCQ Medical records	x	x	x	x
Evaluation of intervention					
Usage of intervention*	Study questionnaire**		x	x	x
Quality of exercises*	Study questionnaire**		x		
Covariates					
Age	Study inclusion form	x			
Severity of pain/discomfort	NRS-11	x			
Treatment expectations	Study questionnaire**	x			

*Only for intervention group.

**The study questionnaires were created specifically for this research.

Abbreviations: NRS-11, Numerical Rating Scale-11; RCADS-25, Revised Anxiety and Depression Scale-25; PBQ, Pain Beliefs Questionnaire; CSI, Children's Somatisation Inventory; EQ-5D-Y, EuroQol Five Dimensions Health Questionnaire Youth; iPCQ, iMTA Productivity Cost Questionnaire; iMCQ, iMTA Medical Consumption Questionnaire.

Primary outcome

The primary outcome is the proportion of children with adequate relief of abdominal pain/discomfort at 12 months. The child or parent(s) are asked whether relief from abdominal pain or discomfort has been adequate during the past week, compared to baseline, on a

dichotomous scale (yes/no). Self-reported adequate relief is a validated outcome measurement in other trials of IBS treatment.[34]

Secondary outcomes

Adequate pain relief at 3 and 6 months

The proportion of children with adequate relief of abdominal pain/discomfort at 3 and 6 months will be assessed using the same dichotomous scale as the primary outcome.

Severity of pain/discomfort

The severity of abdominal pain and/or discomfort in the past week is assessed using an 11-point numerical rating scale (NRS-11) from 0 (no pain) to 10 (worst pain). This scale provides valid and reliable scores in children and adolescents with chronic pain.[35,36]

Pain intensity and frequency

Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,[36] as recommended and often used in other trials of childhood FAP or IBS.[31,36] Pain intensity is assessed using an affective facial pain scale,[37,38] where the faces range from showing no pain at all (score 0) to the most severe pain (score 3). Pain frequency is assessed by asking how long the pain lasted per day, ranging from no pain (score 0) to >2 hours (score 3). The frequency and intensity scores are then totalled for 7 days, giving ranges of 0–21 per score.[26]

Quality of life

The KIDSCREEN-52 is a reliable and valid health-related QoL questionnaire that measures the impact of abdominal pain on daily functioning and QoL.[39-41] It comprises 52 items covering 10 dimensions: physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, relations with parents and home life, social support and peers, school environment, social acceptance (bullying) and financial resources. Participants rate behaviour frequency or attitude intensity in the past week on 5-point Likert scales. Higher scores correspond to better health-related QoL and well-being.

Anxiety and depression

Symptoms of anxiety and depression are assessed by a short version of the Revised Child Anxiety and Depression Scale (RCADS-25), which is a valid and reliable instrument in Dutch populations.[42] The child or parent indicates how often each of the 20 anxiety and 5 depression items applies on 4-point scales from 0 (never) to 3 (always). Higher scores indicate more symptoms of anxiety and/or depression.

Pain beliefs

The paediatric Pain Beliefs Questionnaire (PBQ) includes 32 items that assess beliefs about abdominal pain.[43] Each item consists of a pain belief statement with responses ranging from not true at all (score 0) to very true (score 4). The PBQ comprises three subscales: pain threat (20 items), problem-focused coping efficacy (6 items) and emotion-focused coping efficacy (6 items). A higher score on the pain threat scale indicates a stronger belief that their abdominal pain is a threat. Higher scores on both coping subscales indicate stronger beliefs in their ability to cope with pain using problem- or emotion-focused strategies.

Sleep disturbances

Sleep disturbances are measured using three items from the Dutch Sleep Self Report questionnaire: 'Do you fall asleep in about 20 minutes?' (score reversed), 'Do you wake up at night when your parents think you are asleep?' and 'Do you feel sleepy during the day?'.[44] Children or parents then indicate the frequency in the past week as: rarely (0–1 times), sometimes (2–4 times) and usually (5–7 times). Higher scores indicate more sleep disturbances.

School absence

The cost questionnaire includes an item about school absence in the past 3 months due to abdominal pain/discomfort. Where absence has occurred, they are asked to report the number of days the child actually attended and should have attended.

Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,[45] which includes 35 items on physical symptoms. Scores range from 0 (no problems) to 4 (a lot), and higher scores indicate more somatic complaints. The Dutch version has good psychometric properties.[46]

Cost-utility

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost-utility calculations.[47] It contains a descriptive questionnaire and a visual analogue scale. The descriptive system covers five dimensions (i.e. mobility, self-care, doing usual activities, pain or discomfort, and emotions). Each dimension is rated on three levels: no problems (1 point), some problems (2 points) and a lot of problems (3 points). Children use a visual analogue scale that ranges from 0 to 100 to rate their overall health (ranging from the worst to the best imaginable health). The EQ-5D-Y is feasible, reliable and valid for children aged 8 years and older.[48] Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

Costs

Parents provide information on both medical and non-medical costs using adapted versions of the iMTA Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ).[49] This covers visits to health care providers, prescribed medication and hospital admissions, and out-of-pocket expenses (e.g. over-the-counter medication, child care, productivity losses and travel costs). In addition, researchers screen the medical records of participating children from 3 months before to 12 months after baseline, seeking to identify the number of GP visits, medication prescriptions, referrals to health care providers, hospital admissions and interventions for FAP.

Evaluation of intervention

Usage of intervention

The website is used to collect usage data and measure adherence in the intervention group. This

includes the frequency and duration of intervention use (e.g. when and for how long children log in) plus data on selected exercises (e.g. the exercise chosen and duration). Children are encouraged to attempt the exercises using their own imagination, without listening to the exercises. Children with technical expertise may prefer to listen to the exercises in another way (e.g. downloaded). Given that this is not registered on the website, the follow-up questionnaires include an item about whether and how often children performed the exercises without using the website.

Quality of exercises

At 3 months, children in the intervention group rate the quality of each exercise with an overall score from 0 (bad) to 10 (excellent) and describe what they liked about the exercises and what they think could be improved.

Covariates

The pre-specified covariates are age (<12 and ≥12 years), baseline pain/discomfort severity and treatment expectations. Children and parents are asked to give their expectations of self-hypnosis by rating whether it will improve symptoms on an 11-point scale from 0 (not at all) to 10 (complete recovery). They are also asked whether they have a (strong) preference for either CAU alone or home-based guided hypnotherapy plus CAU.[31]

Sample size calculation

We expect adequate relief in 55% of the CAU group and 75% of the intervention group at 12 months,[3,26] indicating a required difference of 20% to define treatment success. Therefore, a minimum of 90 children per group will be needed to detect treatment success with 80% power at the 5% significance level. Allowing total loss to follow-up of 10%, we aim to include 100 children per group (200 in total).

Statistical analysis

Clinical effectiveness

We will use appropriate descriptive statistics to describe baseline characteristics in both groups. Estimates of treatment effects (proportions, adjusted mean differences or odds ratios, as appropriate) will be presented with 95% confidence intervals and p-values. All outcomes will first be analysed on an intention-to-treat basis, including all children by the group to which they were randomised. We will then perform per-protocol analyses, including children who did not perform hypnotherapy in the control group and children who started at least 4 out of 5 exercises in the intervention group, based on usage data from the website.

The primary outcome will be analysed by logistic multilevel regression modelling, considering relevant covariates. The secondary outcomes will be analysed by logistic (dichotomous variables) and linear (continuous variables) multilevel analyses to investigate the longitudinal relationship between groups. Analysis will be at the patient level for repeated measures in time (baseline, 3, 6 and 12 months), again considering relevant covariates.

Economic evaluation

Costs will be calculated from a societal perspective with a time horizon of 12 months. Health care consumption will be assessed based on current Dutch guidelines for economic evaluation,[50] calculating the cost for use of the intervention website based on the true resources used. We will perform both cost-effectiveness and cost-utility analyses to compare costs and effects between treatment groups. The cost-effectiveness analysis will include the primary outcome, calculating an incremental cost-effectiveness ratio with the added costs or savings expressed per additional patient with adequate symptoms relief. The cost-utility analysis will use the EQ-5D-Y outcome and express the added costs per additional quality-adjusted life year gained. Finally, we will perform bootstrap re-sampling for both cost analyses to produce confidence intervals, and we will plot cost-effectiveness planes and acceptability curves.

Patient and public involvement

We collaborated with the Dutch Child and Hospital Foundation (*Stichting Kind en Ziekenhuis*)

and incorporated their recommendations in the grant proposal, patient information letters and recruitment strategies. They have also agreed to help disseminate our results to the public. The foundation's Child Advisory Board evaluated the user experience of the website before it was finalised for the study. Additionally, we asked eight children with FAP or IBS about the primary outcome and used their recommendations to inform our choice of 'adequate relief' for this purpose.

ETHICS AND DISSEMINATION

Ethical approval and consent to participate

The Medical Ethics Review Committee of the University Medical Center Groningen has reviewed and approved the ZelfHy study (METc2020/237). Protocol amendments are communicated to the ethics committee and participating GPs as needed. To meet the requirements of Dutch law for medical research (*Wet Medisch Onderzoek*), participating GPs are asked to agree to study protocol adherence and either parents (age <12 years), parents and the child (age 12–15 years) or the child only (age 16–17 years) are asked to provide written informed consent (Supplement 3).

Dissemination

Newsletters concerning study progress and any interim results are being disseminated to participants and participating GPs via the study website and e-mail. The study findings will also be presented at (inter)national conferences and published in peer-reviewed journals, ensuring dissemination of the results to relevant stakeholders, such as GPs (NHG), paediatricians (Dutch Association for Child Paediatrics) and patients (Child and Hospital Foundation, Dutch Digestive Foundation and thuisarts.nl). Study data will be made available on request.

DISCUSSION

The home-based guided hypnotherapy provided in this trial represents an eHealth intervention,

delivering or enhancing health services and information through the internet and related technologies.[51] Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,[52-55] proving ideal for use in primary care due to the accessibility and low cost of the exercises. Most adults with IBS prefer remote over face-to-face hypnotherapy, but this has not been studied in children or adolescents.[56] A combination of this eHealth strategy with GP communication and education may help empower patients to take control of their own health and learn to manage their symptoms without the help of others.[57,58] This strategy supports current efforts to help children with functional complaints learn to manage, rather than completely remove, pain. Despite the expected suitability of our intervention for children with FAP or IBS in primary care, several potential issues warrant further discussion.

The primary outcome could raise questions because the European Medicines Agency and Food and Drug Administration recommend using an 11-point NRS as the primary outcome when assessing abdominal pain.[59,60] However, these recommendations are based on studies in adults, with none measuring validity or appropriateness for children. Given that there is also a lack of evidence about the optimal treatment outcome in children, we have based our outcomes on recommendations for clinical trials in children with FAP or IBS. These allow the use of an overall measure of change with treatment, a meaningful clinically important difference and a percentage change in symptoms.[36] We therefore selected adequate relief as our primary outcome, which corresponds to an overall measure of change with treatment, because treatment in primary care aims to reduce the burden of abdominal pain or discomfort (e.g. reducing school absence). Because hypnotherapy aims to reduce both abdominal pain and discomfort, we believe that adequate relief of pain/discomfort is the best outcome measure. Supporting our choice, healthcare professionals, children and parents ranked adequate relief as one of the most important outcome measures.[33]

This trial benefits from using a pragmatic approach characterised by strong applicability and external generalisability to real-world practice. However, this not only has low internal validity due to the lack of blinding and potential for sub-optimal adherence but also precludes etiologic conclusions about the isolated effect of hypnotherapy in primary care.[61,62] To increase our understanding for primary care implementation, we plan to supplement this research with a qualitative evaluation of the acceptability of, and facilitators and barriers related to, home-based guided hypnotherapy.

Recruitment according to our initial protocol was hampered by fewer children than anticipated presenting to GPs with functional abdominal complaints, probably due to a higher threshold to see a GP for non-acute complaints during the covid-19 pandemic. Therefore, we adjusted the recruitment strategy to allow self-referral by children and/or parents. Although this could result in the inclusion of children with less severe complaints, which could in turn influence the primary outcome, we still require that these children visit their GP to optimise comparability. We are keeping track of how patients are recruited to allow later evaluation of differences by the strategy used. Furthermore, we chose to rely on the GP's assessment of FAP or IBS, in line with current practice in primary care, which also increases the external validity in terms of generalisability. Studies in specialist paediatric care often include children with FAP or IBS based on the Rome criteria, which may differ from our study population. However, by measuring the Rome criteria at baseline, we can evaluate differences between children with and without FAP or IBS according to this standard.

In summary, this protocol describes our approach to study the (cost) effectiveness of home-based guided hypnotherapy for children with FAP or IBS in primary care. In the absence of comparable research in this setting, this study could lead to hypnotherapy being recommended as a supplement to GP-delivered CAU and could improve outcomes for these challenging disorders.

AUTHOR'S CONTRIBUTIONS

GAH, MYB, KMV, MAB and AMV conceived the original research concept. ING, TF, HJM-A, AH, ALvdV, KMV, MAB, AMV, MYB and GAH contributed to the study design. ING and ALvdV are responsible for data collection and management during the trial. ING drafted and revised this manuscript. All authors have contributed important intellectual content to the manuscript and have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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REGISTRATION STATEMENT

This study was initially registered in the Dutch Trial Register prior to enrollment of the first participant. Since this register was no longer functional, we additionally registered our study in the ClinicalTrials.gov registry.

EXCLUSIVE LICENCE

REFERENCES

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FIGURE LEGENDS

Figure 1. Study design

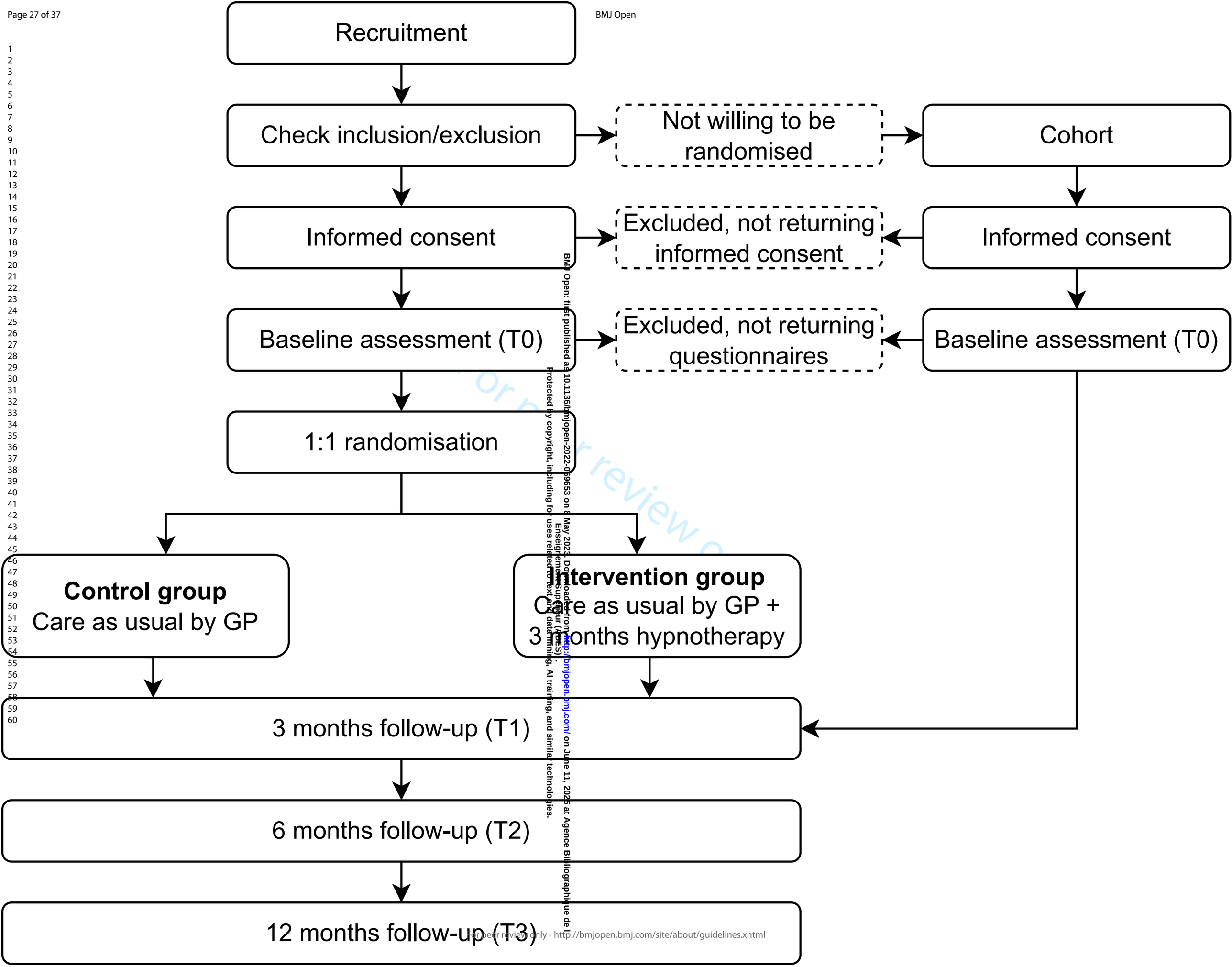
General practitioners screen children for eligibility before randomisation to the control and intervention groups.

SUPPLEMENTAL MATERIAL

Supplement 1. Quick reference card for general practitioners

Supplement 2. International Classification of Primary Care codes for retrospective search

Supplement 3. Informed consent forms



Supplement 1. Quick reference card for general practitioners

REFERENCE CARD OF NHG GUIDELINE HIGHLIGHTS

Definition, epidemiology and diagnostics

Functional abdominal gastrointestinal diseases are '*abdominal pain for which the general practitioner (GP) does not presume underlying tissue damage, somatic causes, or metabolic or anatomic abnormalities based on anamnesis and physical examination*'. The two most important forms are functional abdominal pain and irritable bowel syndrome.

Per norm practice (practice size of 2095 patients) per year, a GP sees on average 10 new children with functional abdominal complaints, more girls than boys. This corresponds with 90% of the children with chronic abdominal pain. Abdominal complaints lasting more than one week increases the chance of functional abdominal pain.

Indication for somatic cause:

- Diarrhoea > 10 days → consider faeces test for parasites
- Indication celiac disease → serologic test or referral to paediatrician
- Indication irritable bowel disease → erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy → pregnancy test

Absence of indication for somatic cause:

- Clinical urine tests to rule out urinary tract infection

Other diagnostics are not recommended.

Rome III criteria in NHG guideline

Functional abdominal pain

1. Recurrent or continue abdominal pain;
2. Abdominal pain ≥ 1 time per week during ≥ 2 months prior to presentation
3. No indication for anatomic, inflammatory, metabolic or neoplastic processes that can explain the abdominal pain

Irritable bowel syndrome

Definition: abdominal pain ≥ 1 time per week during ≥ 2 months, accompanied 1 on 4 times with ≥ 2 of the following:

1. Improvement with defecation
2. Changed defecation frequency
3. Changed stool shape

NHG guideline treatment

Communication – education – reassurance

Education and non-pharmacological treatment:

- Actively involve child and parents/guardians during recovery and policy, adhere to their ideas
- Explain that the gut can oversensitively react to a variety of incentives, that thoughts and feelings can influence the gut and abdomen, and vice versa, abdominal pain influences the emergence of fear and other emotions, and that functional abdominal pain is not a precursor of a dangerous or life-threatening condition.
- Stimulate a balanced diet. Do not recommend extra dietary fibre intake.
- Formulate realistic treatment goals targeting on handling the pain and not on pain disappearance.
- Promote returning to normal activities and regular school attendance.

- Stimulate parents/guardians to pay less attention to the abdominal complaints.
- Choose for complain registration in case of insufficient improvement or recurrent complaints.

Follow-up:

- Follow-up 4 weeks after baseline consultation: discuss the treatment goal and answer questions.
- Advise to return if the character or seriousness of the abdominal pain changes, or if the influence of complaints on activities of daily life increases.

Referral:

- In case of serious persistent functional abdominal pain: discuss additional diagnostics and possible referral with paediatrician.

Hypnotherapy

Medical hypnotherapy is a technique which learns children to gain more control over complaints such as pain and fear, using their own thoughts and fantasies. Research in secondary and tertiary care showed that hypnotherapy by self-exercises helps in 70% of the children.

Supplement 2. International Classification of Primary Care codes for retrospective search

D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D06	Abdominal pain localized other
D11	Diarrhoea
D12	Constipation
D18	Change in faeces/bowel movements
D27	Fear of digestive disease other
D29	Digestive symptom/complaint other
D93	Irritable bowel syndrome
D99	Disease digestive system other

Supplement 3. Informed consent forms

CONSENT FORM PARTICIPANTS

*For participants aged 12-17 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether I want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my participation. I know I do not have to provide a reason.
- I give consent for retrieving my data from my general practitioner.
- I give consent to collect and use my data for the purpose of this research.
- I give consent for collecting my usage data from the website. This includes the number of logins on the website, and which exercises I listened to.
- I know that some persons can look at my data. These persons are mentioned in the patient information letter. I agree that these persons can look at my data.
- I agree to participate in this research.

- I □ do
  □ do not
  give consent to save my data for a maximum of 15 years and use my data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

First and last name: _____

Signature: _____ Date: __/__/____

*Parents of children aged 12-15 years also have to sign 'Consent form Parents/Guardians'

CONSENT FORM PARENTS/GUARDIANS

*For parents of participants aged 7-15 years**

Please fill in the highlighted parts.

Study on treatment of functional abdominal pain in children (ZelfHy study)

I have been asked to give consent for my child's participation in this medically scientific research.

Name participant (child): _____ Date of birth: __/__/____

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether me and my child want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my child's participation. I know I do not have to provide a reason.
- I know that when my child resists this research, my consent for further participation will expire.
- I give consent for retrieving my child's data from my child's general practitioner as mentioned in the patient information letter.
- I give consent to collect and use my child's data for the purpose of this research.
- I give consent to retrieve my child's usage data from the website. This includes the number of logins on the website, and which exercises my child listened to.
- I know that some persons can look at my child's data. These persons are mentioned in the patient information letter. I agree that these persons can look at my child's data.
- I agree that me and my child participate in this research.

- I □ do
  □ do not
  give consent to save my child's data for a maximum of 15 years and use my child's data for comparable scientific research in the future.

- I □ do
  □ do not
  give consent to be approached for future research.

Parent/guardian 1

First and last name: _____

Signature: _____ Date: __/__/____

Parent/guardian 2

First and last name: _____

Signature: _____ Date: __/__/____

*When the child is younger than 16 years, the parents or guardians sign this form. Children between 12 and 15 years also have to sign 'Consent form Participants'

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout manuscript
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8, 9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 9, 10, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14, 15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14, 15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 16, supplement 3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	n.a.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.