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# **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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2	irritable bowel syndrome in primary care: study protocol for a randomised controlled
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### 21 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 homebased 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, peerreviewed 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.

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2 3 4	46	STRENGTHS AND LIMITATIONS OF THIS STUDY
5 6 7	47	• Early management of functional abdominal pain (FAP) and irritable bowel syndrome
8 9	48	(IBS) through home-based guided hypnotherapy may prevent symptoms becoming
10 11	49	chronic.
12 13 14	50	• Exercises are learnt using digital media (eHealth) and fit well with the target population
15 16	51	of young, digitally skilled patients.
17 18	52	• Our pragmatic design has high external generalisability and will provide useful
19 20 21	53	information on the (cost) effectiveness of home-based guided hypnotherapy in a real-
22 23	54	world setting.
24 25 26	55	• The internal validity may be low due to a lack of blinding, with the potential that
26 27 28	56	children in the control group will seek alternative treatment.
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## 57 ABBREVATIONS

- 58 CAU Care as usual
- 59 CSI Children's Somatisation Inventory
- 60 EQ-5D-Y EuroQol Five Dimensions Health Questionnaire Youth
- 61 FAP Functional Abdominal Pain
- 62 GP General practitioner
- 63 IBS Irritable Bowel Syndrome
- 64 iMCQ iMTA Medical Consumption Questionnaire
- 65 iPCQ iMTA Productivity Cost Questionnaire
- 66 NHG *Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
- 7 67 NRS Numerical Rating Scale
- 9 68 PBQ Pain Beliefs Questionnaire
- <sup>1</sup> 69 QoL Quality of Life
- 70 RCADS Revised Anxiety and Depression Scale
- 5 71 REDCap Research Electronic Data Capture
- <sup>3</sup> 72 ZelfHy *ZelfHypnose*; self-hypnosis

#### 74 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.<sup>1-4</sup> These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.<sup>5,6</sup> However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.<sup>7,8</sup> Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,<sup>9</sup> 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.<sup>10</sup> 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.<sup>11-13</sup> 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.<sup>14,15</sup> Around half of these children still report abdominal complaints after 1 year,<sup>3</sup> underlining the difficulty of treatment.

92 Children with FAP or IBS often receive psychosocial interventions in specialist 93 paediatric care due to the strong association between functional symptoms and psychological 94 factors (e.g. stress).<sup>12,13,15-17</sup> Hypnotherapy is one such option that involves a therapist inducing 95 a hypnotic state by guiding a patient to respond to suggestions.<sup>18-20</sup> Studies measuring brain 96 responses in adults with IBS show that hypnotherapy may influence gut motility and normalise 97 visceral sensitivity,<sup>21,22</sup> but the mechanisms behind its effect on functional abdominal

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> symptoms are poorly understood. Nevertheless, research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.<sup>18,19,23</sup> 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.<sup>24</sup> 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 hypotherapy plus CAU will be more (cost) effective for achieving adequate relief from abdominal pain and discomfort in children with FAP or IBS. Lich

#### **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<sup>25</sup> and the extended CONSORT statement for pragmatic trials.<sup>26</sup> 

**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  $\geq 2$  months or  $\geq 2$  episodes in the Page 7 of 36

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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.

#### 128 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.

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Slow recruitment by GPs to 1<sup>st</sup> 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

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version if <12 years, child version if  $\ge$ 12 years).<sup>27</sup> 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.<sup>28</sup> 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.

### 9 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.</li>
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** 

166 Care as usual

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

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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.<sup>29</sup>

We use an existing home-based guided hypnotherapy programme, as described elsewhere,<sup>29</sup> 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 vears 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.

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#### **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.<sup>30</sup> 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  $\geq 12$  years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

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198	Table 1.	Overview	of outcome	parameters	and covariates

Primary outcome	Source	Т0	<b>T1</b>	T2	T
Adequate pain relief at 12 months	Binary yes/no question				x
Secondary outcomes					-
Adequate pain relief at 3 and 6 mont	hs Binary yes/no question		X	x	-
Severity of pain/discomfort	NRS-11	X	X	x	x
Pain frequency and intensity	Abdominal pain diary	X	х	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	х	x	x
Sleep disturbances	Sleep Self Report	X	X	x	x
School absence	Study questionnaire**	X	X	x	x
Somatisation	CSI	X	х	x	x
Utility	EQ-5D-Y	X	х	x	x
Costs	Adjusted iPCQ & iMCQ	X	X	x	x
	Medical records				
Evaluation of intervention	~				
Usage of intervention*	Study questionnaire**		х	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			

\*\*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 60

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

- 212 Secondary outcomes
- 213 Adequate pain relief at 3 and 6 months
- $\frac{2}{3}$  214 The proportion of children with adequate relief of abdominal pain/discomfort at 3 and 6 months
- 215 will be assessed using the same dichotomous scale as the primary outcome.
- 216 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.<sup>32,33</sup>

220 Pain intensity and frequency

Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,<sup>33</sup> as recommended and often used in other trials of childhood FAP or IBS.<sup>29,33</sup> Pain intensity is assessed using an affective facial pain scale,<sup>34,35</sup> 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.<sup>24</sup>

5 228 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.<sup>36-38</sup> It comprises 52 items covering ten dimensions: physical well-being, psychological well-being, moods and emotions, selfperception, 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 Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

236 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.<sup>39</sup> 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.

242 Pain beliefs

The paediatric Pain Beliefs Questionnaire (PBQ) includes 32 items that assess beliefs about abdominal pain.<sup>40</sup> 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.

250 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?'.<sup>41</sup> 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.

256 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.

#### 260 Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,<sup>42</sup> 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.<sup>43</sup>

265 Cost utility

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost utility calculations.<sup>44</sup> 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.<sup>45</sup> Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

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274 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).<sup>46</sup> 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.

<sup>5</sup> 283 Evaluation of intervention

284 Usage of intervention

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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.

295 Covariates

The pre-specified covariates are age (<12 vs.  $\geq$ 12 years), baseline severity of pain/discomfort and treatment expectations. Children and parents are asked to give their expectations of selfhypnosis 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.<sup>29</sup>

<sup>0</sup> 301 **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, <sup>3,24</sup> 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).

- 307 Statistical analysis
- 308 Clinical effectiveness
- <sup>9</sup> 309 We will use appropriate descriptive statistics to describe baseline characteristics in both groups.

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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.

321 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,<sup>47</sup> 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.

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#### 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

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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.

### 341 ETHICS AND DISSEMINATION

#### 342 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.

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#### **DISCUSSION**

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

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#### **BMJ** Open

delivering or enhancing health services and information through the internet and related technologies.<sup>48</sup> Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,<sup>49-52</sup> 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.<sup>53,54</sup> 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.<sup>55,56</sup> 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.<sup>33</sup> 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.<sup>30</sup> 

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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

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> 385 precludes etiologic conclusions about the isolated effect of hypnotherapy in primary care.<sup>57,58</sup> 386 To increase our understanding for primary care implementation, we plan to supplement this 387 research with a qualitative evaluation of the acceptability of, and facilitators and barriers related 388 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.

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# 409 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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## 424 COMPETING INTERESTS STATEMENT

425 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

## 628 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)

1 2		
2 3 4	Supplem	ent 1. International Classification of Primary Care codes for retrospective search
5 6	D01	Abdominal pain/cramps general
7 8	D02	Abdominal pain epigastric
9 10	D06	Abdominal pain localized other
11 12	D11	Diarrhoea
13 14	D12	Constipation
15 16	D18	Change in faeces/bowel movements
17 18	D27	Fear of digestive disease other
19 20 21	D29	Digestive symptom/complaint other
21 22 23	D93	Irritable bowel syndrome
23 24 25	D99	Disease digestive system other
20         27         28         29         30         31         32         33         34         35         36         37         38         39         40         41         42         43         44         45         46         47         48         49         50         51         52         53         54         55         56         57         58         59		teres ont
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# 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  $\rightarrow$  consider faeces test for parasites
- Indication celiac disease  $\rightarrow$  serologic test or referral to paediatrician
- Indication irritable bowel disease  $\rightarrow$  erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy  $\rightarrow$  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  $\geq 1$  time per week during  $\geq 2$  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  $\geq 1$  time per week during  $\geq 2$  months, accompanied 1 on 4 times with  $\geq 2$  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. •

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- 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.

# <mark>□ do</mark>

<mark>□ do not</mark>

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:

I

Signature:

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

Date: / /

Please	fill in the highlighted parts.
Study of	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 resea
Name j	participant (child): Date of birth: _/_/_
- - - - - -	<ul> <li>I have read the patient information letter. It was possible to ask questions. My question sufficiently answered. I had enough time to decide whether me and my child want to participate.</li> <li>I know that my participation is voluntary. I know I can decide at any moment to end me child's participation. I know I do not have to provide a reason.</li> <li>I know that when my child resists this research, my consent for further participation we expire.</li> <li>I give consent for retrieving my child's data from my child's general practitioner as mentioned in the patient information letter.</li> <li>I give consent to collect and use my child's data for the purpose of this research.</li> <li>I give consent to retrieve my child's usage data from the website. This includes the num of logins on the website, and which exercises my child listened to.</li> <li>I know that some persons can look at my child's data. These persons are mentioned in patient information letter. I agree that these persons can look at my child's data.</li> <li>I agree that me and my child participate in this research.</li> </ul>
-	I do
	□ do not give consent to be approached for future research.
Parent	/guardian 1
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<mark>Signatı</mark>	re: Date:/_/_
Parent	/guardian 2
First ar	d last name:

		Standard Protocol Items: Recommendations for Interventional Trials			
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*					
Section/item	ltem No	Description	Addressed on page number		
Administrative information					
Title	1	ਰ ਤੋਂ ਤੋਂ ਕੁੱ Descriptive title identifying the study design, population, interventions, and, if apple ਤਿੰਦੀ ਸ਼ੁੱਵ, trial acronym	1		
rial 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.		
unding	4	Sources and types of financial, material, and other support	19		
Roles and	5a	Names, affiliations, and roles of protocol contributors	1, 19		
responsibilities	5b	Name and contact information for the trial sponsor	1		
	5c	Role of study sponsor and funders, if any, in study design; collection, managemers, agalysis, 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 ove ceing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.		
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			

Page	33 of 36		BMJ Open by coppen	
1 2	Introduction		2022- iright, i	
3 4 5 6 7 8 9 10 11 12 13	Background and rationale	6a	Description of research question and justification for undertaking the trial, includine swommary 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, factors is single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explorations)	6, 8
14 15	Methods: Participants, interventions, and outcomes			
16         17         18         19         20         21         22         23         24         25         26         27         28         29         30         31         32         33         34         35         36         37         38         39         40         41         42         43         44	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of by the settings (eg, community clinic, academic hospital) and list of by the setting 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	دriteria for discontinuing or modifying allocated interventions for a given trial partigipant (eg, drug dose change in response to harms, participant request, or improving/worsening diseas	n.a.
		11c	Strategies to improve adherence to intervention protocols, and any procedures for the 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
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			BMJ Open			
$1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 12 \\ 13 \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ 37 \\ 38 \\ 9 \\ 40 \\ 41 \\ 42 \\ 42 \\ 41 \\ 42 \\ 42 \\ 42 \\ 41 \\ 41$	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was betermined, 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:		es reigr			
	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the provided in a separate document that is unavailable to the second and the second	8		
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequersion between the sequence until interpretion opaque, sealed envelopes), describing any steps to conceal the sequence until interpretions are assigned	8		
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will as sign 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 alidity, 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		
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			
Page 35 of 36			BMJ Open Sp p			
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1 2 3 4	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		
5 6 7	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		
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15		
10 11 12 13		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) statistical methods to handle missing data (eg, multiple imputation)	14, 15		
14 15	Methods: Monitorin	ng	aded 1 and			
16 17 18 19 20 21 22 23 24	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report from the sponsor and competing interests; and reference where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of whether it is 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.		
25 26 27	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously eported adverse events and other unintended effects of trial interventions or trial conduct	8		
28 29 30 31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process bill be independent from investigators and the sponsor	n.a.		
32 33	Ethics and dissemi	ination	gies.			
34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) ap	16		
37 38 39 40 41 42	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creeria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals, regulators)	16		
43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			

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			BMJ Open Coppe	Page 3	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or autre d surrogates, and 7, 8, 16, how (see Item 32)	3	
		26b	Additional consent provisions for collection and use of participant data and biological goecimens in ancillary n.a.		
	Confidentiality	27	How personal information about potential and enrolled participants will be collected and ared, and maintained 8 in order to protect confidentiality before, during, and after the trial		
	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall transford each study site 19		
	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contract all agreements that 19 limit such access for investigators		
	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those where suffer harm from trial n.a.		
	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, 16 the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		
		31b	Authorship eligibility guidelines and any intended use of professional writers		
	<b>A</b>	31c	Plans, if any, for granting public access to the full protocol, participant-level datas and statistical code 16		
	Appendices		achine 11		
	Informed consent materials	32	Model consent form and other related documentation given to participants and aughors des Supplement	3	
	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for generative or molecular n.a. analysis in the current trial and for future use in ancillary studies, if applicable		
	*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.				
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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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Keywords:	PRIMARY CARE, Functional bowel disorders < GASTROENTEROLOGY, Paediatric gastroenterology < PAEDIATRICS

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1	Home-based guided hypnotherapy for children with functional abdominal pain and
2	irritable bowel syndrome in primary care: study protocol for a randomised controlled
3	trial
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#### 21 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 homebased 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).

39 Ethics and dissemination: The Medical Ethics Review Committee of the University Medical 40 Center Groningen, the Netherlands, approved this study (METc2020/237). The results will be 41 disseminated to patients, GPs and other stakeholders via e-mail, a dedicated website, peer-42 reviewed publications and presentations at national and international conferences. We plan to 43 collaborate with the Dutch Society of GPs to implement the results in clinical practice.

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

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2 3 4	46	STRENGTHS AND LIMITATIONS OF THIS STUDY
5 6 7	47	• Early management of functional abdominal pain (FAP) and irritable bowel syndrome
8 9	48	(IBS) through home-based guided hypnotherapy may prevent symptoms becoming
10 11	49	chronic.
12 13 14	50	• Exercises are learnt using digital media (eHealth) and fit well with the target population
15 16	51	of young, digitally skilled patients.
17 18	52	• Our pragmatic design has high external generalisability and will provide useful
19 20 21	53	information on the (cost) effectiveness of home-based guided hypnotherapy in a real-
22 23	54	world setting.
24 25	55	• The internal validity may be low due to a lack of blinding, with the potential that
26 27 28	56	children in the control group will seek alternative treatment.
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## 57 ABBREVATIONS

- 58 CAU Care as usual
- 59 CSI Children's Somatisation Inventory
- 60 EQ-5D-Y EuroQol Five Dimensions Health Questionnaire Youth
- 61 FAP Functional Abdominal Pain
- 62 GP General practitioner
- 63 IBS Irritable Bowel Syndrome
- 64 iMCQ iMTA Medical Consumption Questionnaire
- 65 iPCQ iMTA Productivity Cost Questionnaire
- 66 NHG *Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
- 7 67 NRS Numerical Rating Scale
- 9 68 PBQ Pain Beliefs Questionnaire
- <sup>1</sup> 69 QoL Quality of Life
- 70 RCADS Revised Anxiety and Depression Scale
- 5 71 REDCap Research Electronic Data Capture
- <sup>3</sup> 72 ZelfHy *ZelfHypnose*; self-hypnosis

#### 74 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.<sup>1-4</sup> These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.<sup>5,6</sup> However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.<sup>7,8</sup> Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,<sup>9</sup> 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.<sup>10</sup> 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.<sup>11-13</sup> 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.<sup>14,15</sup> Around half of these children still report abdominal complaints after 1 year,<sup>3</sup> underlining the difficulty of treatment.

92 Children with FAP or IBS often receive psychosocial interventions in specialist 93 paediatric care due to the strong association between functional symptoms and psychological 94 factors (e.g. stress).<sup>12,13,15-17</sup> Hypnotherapy is one such option that involves a therapist inducing 95 a hypnotic state by guiding a patient to respond to suggestions.<sup>18-20</sup> Studies measuring brain 96 responses in adults with IBS show that hypnotherapy may influence gut motility and normalise 97 visceral sensitivity,<sup>21,22</sup> but the mechanisms behind its effect on functional abdominal

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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.<sup>23</sup> Indeed, hypnotherapy should always be performed by a trained professional.<sup>24,25</sup> Research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.<sup>18,19,24</sup> 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.<sup>26</sup> 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.

110 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.

- 114 114
- **METHODS AND ANALYSIS** 
  - 116 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<sup>27</sup> and the extended CONSORT statement for pragmatic trials.<sup>28</sup>

## **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  $\geq 2$  months or  $\geq 2$  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.<sup>14</sup> 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.

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Slow recruitment by GPs to 1<sup>st</sup> 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

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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.

151 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  $\geq$ 12 years).<sup>29</sup> 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.<sup>30</sup> 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. 

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## 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  $\geq$ 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

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5 6 7	174	Care as usual
7 8 9	175	All children receive CAU by their GP according to the NHG guideline for abdominal pain in
10 11	176	children, <sup>14</sup> offering communication, education and reassurance. The guideline advocates
12 13	177	realistic treatment goals that focus on pain management, rather than pain resolution, and follow-
14 15 16	178	up. Since this is a pragmatic trial, we do not restrict GPs in giving any form of treatment because
17 18	179	GPs know best what the patient needs. Supplement 1 illustrates an overview of the guideline
19 20 21	180	highlights, which is provided to all participating GPs.
21 22 23	181	
24 25	182	Hypnotherapy by self-exercises
26 27	183	Children in the intervention group are asked to perform home-based guided hypnotherapy for
28 29 30	184	3 months, supplemented with CAU by their GP. Prior to starting the exercises, a researcher
31 32	185	arranges an online video call with the child and parent(s) to explain hypnotherapy, how it can
33 34	186	help reduce abdominal pain and how they can access the exercises. Additionally, the child and
35 36 37	187	parent(s) are instructed not to discuss the pain anymore. <sup>31</sup>
38 39	188	We use an existing home-based guided hypnotherapy programme, as described
40 41	189	elsewhere, <sup>31</sup> adjusted for this study. This comprises one breathing and progressive relaxation
42 43	190	exercise and four visualisation exercises: 'the favourite place', 'the rainbow planet' or 'air
45 46	191	balloon' (depending on age version), 'the beach without worries', and 'the slide'. Exercises
47 48	192	have been recorded by a hypnotherapist in a digital audio format (MP3). In Table 1, examples
49 50 51	193	of hypnotic suggestions are displayed. The language is adapted to the child's age, with one
52 53	194	version each for children aged <12 years and $\geq$ 12 years. The intensity, i.e. duration of each
54 55	195	exercise is equal for both versions, and feasible for all age groups. <sup>31,32</sup> We include the
56 57	196	instructions and exercises for both versions in a newly designed, responsive, login-protected

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website. Instructions are directly visible on the home page and vary each week. For example,

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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.

205 **Table 1**. Examples of hypnotic suggestions

Aim	Examples of hypnotic suggestions
Normalising gut	"Every day, by practicing your deep breathing, slowly in and out, your belly will
functions	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, pffff, 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	

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#### 207 **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.<sup>33</sup> 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  $\geq$ 12 years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

Primary outcome	Source	TO	T1	T2	T:
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	NPS 11	v	v	v	v
Seventy of pain/disconnort	1185-11	Λ	Λ	^	^
Pain frequency and intensity	Abdominal pain diary	х	х	х	x
Daily functioning and impact	KIDSCREEN-52	x	x	x	x
Anxiety and depression	RCADS-25	Х	Х	X	X
Pain beliefs	PBQ	X	x	x	x
Slean disturbances	Sleen Solf Depart			**	
Sleep disturbances	Sleep Sell Report	X	X	X	X
School absence	Study questionnaire**	X	X	x	X
Sometisation	CSI	v	v	v	v
Somatisation	CSI	Λ	Λ	Λ	^
Utility	EQ-5D-Y	х	х	х	x
Costs	Adjusted iPCO & iMCO	X	x	x	x
	Medical records				
<b>Evaluation of intervention</b>					
Usage of intervention*	Study questionnaire**		v	v	v
	Study questionnune		Λ	Λ	^
Quality of exercises*	Study questionnaire**		х		
Covariates					-
A ~~	Study in church of forme				
Age	Study inclusion form	X			
Severity of pain/discomfort	NRS-11	X			
Treatment expectations	Study questionnaire**	X			-
 1					

216	Table 2. Overview of outcome parameters and co	variates
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\*\*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 

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dichotomous scale (yes/no). Self-reported adequate relief is a well validated outcome

measurement in other trials of IBS treatment.<sup>34</sup>

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.<sup>35,36</sup> *Pain intensity and frequency* Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,<sup>36</sup> as recommended and often used in other trials of childhood FAP or IBS.<sup>31,36</sup> Pain intensity is assessed using an affective facial pain scale,<sup>37,38</sup> 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.<sup>26</sup> 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.<sup>39-41</sup> 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 

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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.<sup>42</sup> 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.<sup>43</sup> 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.

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*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?'.<sup>44</sup> 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. 

#### 278 Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,<sup>45</sup> 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.<sup>46</sup>

283 Cost utility

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost utility calculations.<sup>47</sup> 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.<sup>48</sup> Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

292 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).<sup>49</sup> 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. 

- 56 301 Evaluation of intervention
  57
  - 302 Usage of intervention

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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.

315 Covariates

The pre-specified covariates are age (<12 vs.  $\geq$ 12 years), baseline severity of pain/discomfort and treatment expectations. Children and parents are asked to give their expectations of selfhypnosis 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.<sup>31</sup> Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

## 5 321 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, <sup>3,26</sup> 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).

59 327 Statistical analysis
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## 328 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.

<sup>3</sup> 341 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,<sup>50</sup> 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** 

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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.

## 361 ETHICS AND DISSEMINATION

## 362 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**

<sup>45</sup> 371 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
 <sup>47</sup> 372 presented at (inter)national conferences and published in peer-reviewed journals, ensuring the
 <sup>52</sup> 374 dissemination of the results to relevant stakeholders, such as GPs (NHG), paediatricians (Dutch
 <sup>54</sup> 375 Association for Child Paediatrics) and patients (Child and Hospital Foundation, Dutch
 <sup>56</sup> Digestive Foundation and thuisarts.nl). Study data will be made available on request.

<sup>59</sup> 377 **DISCUSSION** 

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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.<sup>51</sup> Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,<sup>52-55</sup> 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.<sup>56</sup> 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.<sup>57,58</sup> 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.<sup>59,60</sup> 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.<sup>36</sup> 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

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403 one of the most important outcome measures.<sup>33</sup>

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.<sup>61,62</sup> 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.

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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 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

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AUTHOR'S CONTRIBUTIONS

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manuscript and have read and approved the final manuscript.

**COMPETING INTERESTS STATEMENT** 

The authors declare no competing interests.

**FUNDING STATEMENT** 

#### 20

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## 453 REGISTRATION STATEMENT

454 This study was initially registered in the Dutch Trial Register prior to enrollment of the first 455 participant. Since this register was no longer functional, we additionally registered our study in 456 the ClinicalTrials.gov registry.

- - 458 EXCLUSIVE LICENCE

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2 3 4	672	FIGURE LEGENDS
5 6	673	Figure 1. Study design
/ 8 9	674	General practitioners screen children for eligibility before randomisation to the control and
10 11	675	intervention groups.
12 13	676	
14 15 16	677	SUPPLEMENTAL MATERIAL
17 18 10	678	Supplement 1. Quick reference card for general practitioners
19 20 21	679	Supplement 2. International Classification of Primary Care codes for retrospective search
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# 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 <u>functional abdominal pain</u> and <u>irritable bowel syndrome</u>.

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:

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- Diarrhoea > 10 days  $\rightarrow$  consider faeces test for parasites
- Indication celiac disease  $\rightarrow$  serologic test or referral to paediatrician
- Indication irritable bowel disease → erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy  $\rightarrow$  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  $\geq 1$  time per week during  $\geq 2$  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  $\ge 1$  time per week during  $\ge 2$  months, accompanied 1 on 4 times with  $\ge 2$  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.

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## 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

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data mining, AI training, and similar technologies

CONS	ENT FORM PARTICIPANTS
For pa	rticipants aged 12-17 years*
Please	fill in the highlighted parts.
<u>Study c</u>	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 ar 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 agree to participate in this research. I agree 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 ar	d last name:
Signati	re: Date: / /
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*Paren	s of children aged 12-15 years also have to sign 'Consent form Parents/Guardians'

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1 10050 1111 1	in the inglinghted parts.	
Study on tr	reatment of functional abdominal pain in children (ZelfHy study)	
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Name parti	icipant (child): Date of birth:/_	/
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		SPIRIT IN TOTAL STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS		
SPIRIT 2013 Chec	klist: Rec	ommended items to address in a clinical trial protocol and related documents*		
Section/item	ltem No	Description	Addressed on page number	
Administrative inf	formation	nloadec t Super text an		
Title	1	Descriptive title identifying the study design, population, interventions, and, if apple above, trial acronym	1	
Frial 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.	
unding	4	Sources and types of financial, material, and other support	19	
Roles and	5a	Names, affiliations, and roles of protocol contributors	1, 19	
responsibilities	5b	Name and contact information for the trial sponsor	1	
	5c	Role of study sponsor and funders, if any, in study design; collection, managemers, as alysis, 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 ove seeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		
			BMJ Open by copyri	Page 34 of 37
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1 2	Introduction		ght, i	
3 4 5	Background and rationale	6a	Description of research question and justification for undertaking the trial, includin a some and relevant 5, 6 studies (published and unpublished) examining benefits and harms for each intergention	
6 7		6b	Explanation for choice of comparators	
8 9	Objectives	7	Specific objectives or hypotheses 6	
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factoria single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explorations) 6, 8 يَوْ يَوْمَ	
14 15	Methods: Participa	nts, int	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of by the study settings (eg, community clinic, academic hospital) and list of gradient study sites can be obtained	
19 20 21	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 6, 7 individuals who will perform the interventions (eg, surgeons, psychotherapists)	
22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including ho and when they will be 8, 9 administered	
23 26 27 28		11b	Criteria for discontinuing or modifying allocated interventions for a given trial parti الصفية (eg, drug dose n.a. change in response to harms, participant request, or improving/worsening diseas المجيع المج	
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for the monitoring adherence 8, 9 (eg, drug tablet return, laboratory tests)	
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial n.a.	
34 35 36 37 38	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, 9-14 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
39 40 41 42	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 7, 9, 10, I participants. A schematic diagram is highly recommended (see Figure)	Figure 1
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2

Page	35 of 37		BMJ Open Sp	
1 2	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was betermined, including clinical and statistical assumptions supporting any sample size calculations	14
3 4 5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
6 7	Methods: Assignm	ent of i	nterventions (for controlled trials)	
8 9	Allocation:		ay 202 Ses reig	
10 11 12 13 14 15	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be the sequence), and list of any factors for stratification. To reduce predictability of a random sequence, details of a separate document that is unavailable to the sequence participants or assign interventions	8
16 17 18 19	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequerite is ly numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until in the mentions are assigned	8
20 21 22 22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
23 24 25 26	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
27 28 29		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
30 31	Methods: Data coll	ection,	management, and analysis	
32 33 34 35 36 37	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
38 39 40 41		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
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4	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
5 6 7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to $\vec{a}$ here $\vec{b}$ of the statistical analysis plan can be found, if not in the protocol	14, 15
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15
10 11 12 13		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomined analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14, 15
14 15	Methods: Monitorir	ng	and of the second se	
16 17 18 19 20	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report fructure; statement of whether it is independent from the sponsor and competing interests; and reference whether further details about its charter can be found, if not in the protocol. Alternatively, an explanation of whether it is needed	n.a.
21 22 23 24		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.
25 26 27	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously peported adverse events and other unintended effects of trial interventions or trial conduct	8
28 29 30 31	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.
32 33	Ethics and dissemi	nation	ging 25 es at	
34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) apla oval	16
37 38 39 40 41 42	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creations, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals, regulators)	16
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

Page	37 of 37		BMJ Open Sp pg	
1 2	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
3 4 5 6		26b	Additional consent provisions for collection and use of participant data and biolog	n.a.
7 8 9	Confidentiality	27	How personal information about potential and enrolled participants will be collected and ared, and maintained in order to protect confidentiality before, during, and after the trial	8
10 11 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall transford each study site	19
13 14 15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contracteal agreements that limit such access for investigators	19
16 17 18 10	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those where suffer harm from trial participation	n.a.
20 21 22 23	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health are professionals, the public, and other relevant groups (eg, via publication, reporting in results data as s, or other data sharing arrangements), including any publication restrictions	16
24 25		31b	Authorship eligibility guidelines and any intended use of professional writers	n.a.
26 27 28		31c	Plans, if any, for granting public access to the full protocol, participant-level datas and statistical code	16
29 30	Appendices		ee 11,	
31 32 33	Informed consent materials	32	Model consent form and other related documentation given to participants and autoobsed surrogates	Supplement 3
34 35 36	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for generatic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.
37 38 39 40 41 42 43 44 45	*It is strongly recomm Amendments to the p " <u>Attribution-NonComm</u>	nended protocol <u>mercial-</u>	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Convolution of the second structure of the secon	ation on the items. ommons

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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

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-069653.R2
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Date Submitted by the Author:	03-Mar-2023
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<b>Primary Subject Heading</b> :	General practice / Family practice
Secondary Subject Heading:	Paediatrics
Keywords:	PRIMARY CARE, Functional bowel disorders < GASTROENTEROLOGY, Paediatric gastroenterology < PAEDIATRICS

# SCHOLARONE<sup>™</sup> Manuscripts

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1	Home-based guided hypnotherapy for children with functional abdominal pain and
2	irritable bowel syndrome in primary care: study protocol for a randomised controlled
3	trial
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## 21 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

39 Center Groningen, the Netherlands, approved this study (METc2020/237). The results will be 40 disseminated to patients, GPs and other stakeholders via e-mail, a dedicated website, peer-41 reviewed publications and presentations at national and international conferences. We plan to 42 collaborate with the Dutch Society of GPs to implement the results in clinical practice.

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

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2 3 4	45	STRENGTHS AND LIMITATIONS OF THIS STUDY
5 6 7	46	• Early management of functional abdominal pain (FAP) and irritable bowel syndrome
, 8 9	47	(IBS) through home-based guided hypnotherapy may prevent symptoms becoming
10 11	48	chronic.
12 13	49	• Exercises are learnt using digital media (eHealth) and fit well with the target population
14 15 16	50	of young, digitally skilled patients.
17 18	51	• Our pragmatic design has high external generalisability and will provide useful
19 20 21	52	information on the (cost) effectiveness of home-based guided hypnotherapy in a real-
21 22 23	53	world setting.
24 25	54	• The internal validity may be low due to a lack of blinding, with the potential that
26 27 28	55	children in the control group will seek alternative treatment.
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## 56 ABBREVATIONS

- CAU Care as usual
- 58 CSI Children's Somatisation Inventory
- 59 EQ-5D-Y EuroQol Five Dimensions Health Questionnaire Youth
- 60 FAP Functional Abdominal Pain
- 61 GP General practitioner
- 62 IBS Irritable Bowel Syndrome
- 63 iMCQ iMTA Medical Consumption Questionnaire
- 64 iPCQ iMTA Productivity Cost Questionnaire
- 65 NHG *Nederlands Huisartsen Genootschap*; Dutch Society of General Practitioners
- <sup>o</sup> 66 NRS Numerical Rating Scale
- 9 67 PBQ Pain Beliefs Questionnaire
- <sup>1</sup> 68 QoL Quality of Life
- 69 RCADS Revised Anxiety and Depression Scale
- 6 70 REDCap Research Electronic Data Capture
- <sup>3</sup> 71 ZelfHy *ZelfHypnose*; self-hypnosis

## 72 INTRODUCTION

## 73 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.<sup>1-4</sup> These disorders are associated with reduced quality of life (QoL), school absence, sleep disturbances, anxiety and depression.<sup>5,6</sup> However, our limited understanding of their exact pathophysiology and the role of multiple factors in maintaining the complaints can make their management challenging.<sup>7,8</sup> Given that secondary healthcare use and parental productivity loss appear to drive the estimated annual healthcare costs of €2,512 per child,<sup>9</sup> 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.<sup>10</sup> 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.<sup>11-13</sup> 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.<sup>14,15</sup> Around half of these children still report abdominal complaints after 1 year,<sup>3</sup> underlining the difficulty of treatment.

91 Children with FAP or IBS may receive psychosocial interventions in specialist 92 paediatric care due to the strong association between functional symptoms and psychological 93 factors (e.g. stress).<sup>12,13,15-17</sup> Hypnotherapy is one such option that involves a therapist inducing 94 a hypnotic state by guiding a patient to respond to suggestions.<sup>18-20</sup> Studies measuring brain 95 responses in adults with IBS show that hypnotherapy may influence gut motility and normalise 96 visceral sensitivity,<sup>21,22</sup> though the mechanisms behind its effect on functional abdominal

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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.<sup>23</sup> Indeed, hypnotherapy should always be performed by a trained professional.<sup>24,25</sup> Research in children and adolescents has found that hypnotherapy significantly reduces abdominal pain and symptom scores.<sup>18,19,24</sup> 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.<sup>26</sup> 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.

109 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.

- 113 lu
- <sup>2</sup> 114 **METHODS AND ANALYSIS** 
  - 115 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<sup>27</sup> and the extended CONSORT statement for pragmatic trials.<sup>28</sup>

## 122 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  $\geq 2$  months or  $\geq 2$  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.<sup>14</sup> 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) 

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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  $\ge 12$  years).<sup>29</sup> 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.<sup>30</sup> 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.

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## 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  $\geq$ 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.

172	Intervention
173	Care as usual

All children receive GP-based CAU according to the NHG guideline for abdominal pain in children,<sup>14</sup> 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.<sup>31</sup> 

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We use an existing home-based guided hypnotherapy programme, as described elsewhere,<sup>31</sup> 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  $\geq$ 12 years. Both versions are of equal intensity (e.g., exercise duration) and are feasible for all relevant age groups.<sup>31,32</sup> 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

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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	"Every day, by practicing your deep breathing, slowly in and out, your belly will
functions	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.<sup>33</sup> 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  $\leq 12$  years, while children aged  $\geq 12$  years complete the questionnaires themselves, with parental help as needed. Parents always complete the costs questionnaires.

Primary outcome	Source	TO	T1	T2	T
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		v	v	
				~	
Severity of pain/discomfort	NRS-11	Х	х	х	X
Pain frequency and intensity	Abdominal pain diary	X	х	х	x
Daily functioning and impact	KIDSCREEN-52	x	X	X	X
Anxiety and depression	RCADS-25	X	X	X	x
Pain beliefs	PBO	x	X	x	X
Sleep disturbances	Sleen Self Report	x	x	x	X
School absorption	Study questionnoire**				
School absence	Study questionnane.	X	X	X	2
Somatisation	CSI	Х	x	x	2
Utility	EQ-5D-Y	X	X	X	X
Costs	Adjusted iPCQ & iMCQ	x	X	X	X
	Medical records				
Evaluation of intervention					
Usage of intervention*	Study questionnaire**		x	x	X
Quality of exercises*	Study questionnaire**		x		-
Coverietes	Study questionnune				
Covariates					
Age	Study inclusion form	X			
Severity of pain/discomfort	NRS-11	x			1
Treatment expectations	Study questionnaire**	v			-
	Adequate pain relief at 12 monthsSecondary outcomesAdequate pain relief at 3 and 6 monthsSeverity of pain/discomfortPain frequency and intensityDaily functioning and impactAnxiety and depressionPain beliefsSleep disturbancesSchool absenceSomatisationUtilityCostsEvaluation of interventionUsage of intervention*Quality of exercises*AgeSeverity of pain/discomfort	Frinary outcomeSourceAdequate pain relief at 12 monthsBinary yes/no questionSecondary outcomesImage: Adequate pain relief at 3 and 6 monthsBinary yes/no questionSeverity of pain/discomfortNRS-11Pain frequency and intensityAbdominal pain diaryDaily functioning and impactKIDSCREEN-52Anxiety and depressionRCADS-25Pain beliefsPBQSleep disturbancesSleep Self ReportSchool absenceStudy questionnaire**SomatisationCSIUtilityEQ-5D-YCostsAdjusted iPCQ & iMCQ Medical recordsEvaluation of interventionStudy questionnaire**Quality of exercises*Study questionnaire**AgeStudy inclusion form NRS-11	Frinary outcomeSourceForAdequate pain relief at 12 monthsBinary yes/no questionSecondary outcomesAdequate pain relief at 3 and 6 monthsBinary yes/no questionSeverity of pain/discomfortNRS-11xPain frequency and intensityAbdominal pain diaryxDaily functioning and impactKIDSCREEN-52xAnxiety and depressionRCADS-25xPain beliefsPBQxSleep disturbancesSleep Self ReportxSchool absenceStudy questionnaire**xCostsAdjusted iPCQ & iMCQ Medical recordsxUtilityEQ-5D-YxQuality of exercises*Study questionnaire**Quality of exercises*Study questionnaire**AgeStudy inclusion formxSeverity of pain/discomfortNRS-11x	Frimary outcomeSourceForFriAdequate pain relief at 12 monthsBinary yes/no questionSecondary outcomesAdequate pain relief at 3 and 6 monthsBinary yes/no questionSeverity of pain/discomfortNRS-11xxPain frequency and intensityAbdominal pain diaryxxDaily functioning and impactKIDSCREEN-52xxAnxiety and depressionRCADS-25xxPain beliefsPBQxxSchool absenceStudy questionnaire**xxSomatisationCSIxxUtilityEQ-5D-YxxCostsAdjusted iPCQ & iMCQ Medical recordsxxQuality of exercises*Study questionnaire**xxQuality of pain/discomfortNRS-11xx	Frinary outcomeSourceIoIII2Adequate pain relief at 12 monthsBinary yes/no questionSecondary outcomesAdequate pain relief at 3 and 6 monthsBinary yes/no questionxxSeverity of pain/discomfortNRS-11xxxxPain frequency and intensityAbdominal pain diaryxxxxDaily functioning and impactKIDSCREEN-52xxxxAnxiety and depressionRCADS-25xxxxSleep disturbancesSleep Self ReportxxxxSchool absenceStudy questionnaire**xxxxCostsAdjusted iPCQ & iMCQ Medical recordsxxxxUsage of intervention*Study questionnaire**xxxQuality of exercises*Study inclusion formxxxAgeStudy inclusion formxxx

214	Table 2. Overview of outcome parameters and covariates
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\*\*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 

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

228 Secondary outcomes

229 Adequate pain relief at 3 and 6 months

 $\frac{12}{13}$  230 The proportion of children with adequate relief of abdominal pain/discomfort at 3 and 6 months

231 will be assessed using the same dichotomous scale as the primary outcome.

232 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.<sup>35,36</sup>

26
27
236 Pain intensity and frequency

Participants record their abdominal pain or discomfort for seven consecutive days in a diary to aid recall,<sup>36</sup> as recommended and often used in other trials of childhood FAP or IBS.<sup>31,36</sup> Pain intensity is assessed using an affective facial pain scale,<sup>37,38</sup> 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.<sup>26</sup> 

243 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.<sup>39-41</sup> 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. 

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## 251 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.<sup>42</sup> 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.

## 257 Pain beliefs

The paediatric Pain Beliefs Questionnaire (PBQ) includes 32 items that assess beliefs about abdominal pain.<sup>43</sup> 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. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

*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?'.<sup>44</sup> 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.

275 Somatisation

We use the Children's Somatisation Inventory (CSI) to assess somatisation,<sup>45</sup> 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.<sup>46</sup>

*Cost-utility* 

The generic EuroQoL Youth (EQ-5D-Y) is being used for the cost-utility calculations.<sup>47</sup> 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.<sup>48</sup> Parents of children aged <12 years receive and complete a proxy version of the questionnaire.

33 289 *Costs* 34

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).<sup>49</sup> 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. 

54 298 Evaluation of intervention

299 Usage of intervention

 $_{59}^{58}$  300 The website is used to collect usage data and measure adherence in the intervention group. This

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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.

308 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.

312 Covariates

The pre-specified covariates are age (<12 and  $\geq 12$  years), baseline pain/discomfort severity and treatment expectations. Children and parents are asked to give their expectations of selfhypnosis 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.<sup>31</sup>

<sup>2</sup> 318 Sample size calculation

We expect adequate relief in 55% of the CAU group and 75% of the intervention group at 12 months,<sup>3,26</sup> 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).

- 57 324 Statistical analysis
- 59 325 Clinical effectiveness

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> 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.

338 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,<sup>50</sup> 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.

<sup>6</sup><sub>7</sub> 349 **Patient and public involvement** 

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

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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).

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#### 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,

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delivering or enhancing health services and information through the internet and related technologies.<sup>51</sup> Moreover, eHealth for psychological interventions represents an emerging clinical resource when treating children and adolescents with chronic diseases,<sup>52-55</sup> 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.<sup>56</sup> 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.<sup>57,58</sup> 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.<sup>59,60</sup> 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.<sup>36</sup> 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 

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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.<sup>61,62</sup> 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.

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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.

2 3 4	426		
5 6 7	427	AUTHOR'S CONTRIBUTIONS	
, 8 9	428	GAH, MYB, KMV, MAB and AMV conceived the original research concept. ING, TF, HJM-	
10 11	429	A, AH, ALvdV, KMV, MAB, AMV, MYB and GAH contributed to the study design. ING and	
12 13	430	ALvdV are responsible for data collection and management during the trial. ING drafted and	
14 15 16	431	revised this manuscript. All authors have contributed important intellectual content to the	
17 18	432	manuscript and have read and approved the final manuscript.	
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38 39			
40 41 42			
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57 58	449		
59 60	450	REGISTRATION STATEMENT	

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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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3 4	669	FIGURE LEGENDS
5 6 7	670	Figure 1. Study design
7 8 9	671	General practitioners screen children for eligibility before randomisation to the control and
10 11	672	intervention groups.
12 13	673	
14 15 16	674	SUPPLEMENTAL MATERIAL
17 18	675	Supplement 1. Quick reference card for general practitioners
19 20 21	676	Supplement 2. International Classification of Primary Care codes for retrospective search
22 23	677	Supplement 3. Informed consent forms
25 26 27 28 29 30 31 32 33 4 35 36 37 38 39 40 41 42 43 44 56 47 48 49 50 51 52 53 54 55 60		



# 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 <u>functional abdominal pain</u> and <u>irritable bowel syndrome</u>.

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:

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- Diarrhoea > 10 days  $\rightarrow$  consider faeces test for parasites
- Indication celiac disease  $\rightarrow$  serologic test or referral to paediatrician
- Indication irritable bowel disease → erythrocyte sedimentation rate, leucocyte or haemoglobin test
- Possible pregnancy  $\rightarrow$  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  $\geq 1$  time per week during  $\geq 2$  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  $\ge 1$  time per week during  $\ge 2$  months, accompanied 1 on 4 times with  $\ge 2$  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.

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## 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

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CONS	ENT FORM PARTICIPANTS	
For pa	rticipants aged 12-17 years*	
Please	fill in the highlighted parts.	
<u>Study c</u>	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 ar 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 agree to participate in this research. I agree to save my data for a maximum of 15 years and use my data for comparable scientific research in the future.	
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		SPIRIT IN TOTAL STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS	
SPIRIT 2013 Chec	klist: Rec	ommended items to address in a clinical trial protocol and related documents*	
Section/item	ltem No	Description	Addressed on page number
Administrative inf	formation	nloadec t Super text an	
Title	1	Descriptive title identifying the study design, population, interventions, and, if apple above, trial acronym	1
Frial 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.
unding	4	Sources and types of financial, material, and other support	19
Roles and	5a	Names, affiliations, and roles of protocol contributors	1, 19
responsibilities	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, managemers, as alysis, 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 ove decing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2	Introduction		ght, i				
3 4 5 6 7 8 9 10 11 12 13	Background and rationale	6a	Description of research question and justification for undertaking the trial, includine signmary of relevant 5, 6 studies (published and unpublished) examining benefits and harms for each intergention				
		6b	Explanation for choice of comparators 약 👼 6				
	Objectives	7	Specific objectives or hypotheses 6				
	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, face and single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explorations) 6, 8				
14 15	Methods: Participants, interventions, and outcomes						
16 17 18 19 20 21	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of appendictions where data will 6 be collected. Reference to where list of study sites can be obtained				
	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 6, 7 individuals who will perform the interventions (eg, surgeons, psychotherapists)				
22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including hoថ្មី ard when they will be 8, 9 administered				
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42		11b	Criteria for discontinuing or modifying allocated interventions for a given trial parti and the second seco				
		11c	Strategies to improve adherence to intervention protocols, and any procedures for to intervence 8, 9 (eg, drug tablet return, laboratory tests)				
		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, 9-14 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended				
	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 7, 9, 10, Fi participants. A schematic diagram is highly recommended (see Figure)	gure 1			
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2			

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1 2	Sample size	14	돌 확 Estimated number of participants needed to achieve study objectives and how it was betermined, including clinical and statistical assumptions supporting any sample size calculations 글 않	14	
3 4 5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7	
6 7	Methods: Assignm	ent of i	nterventions (for controlled trials)		
8 9	Allocation:		ses rel		
10 11 12 13 14 15 16 17 18 19 20 21 22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be been been been been been been been	8	
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequerite in the sequence until the sequence until in the	8	
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8	
23 24 25 26	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8	
27 28 29		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.	
30 31	Methods: Data collection, management, and analysis				
32 33 34 35 36 37	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 alidity, if known. Reference to where data collection forms can be found, if not in the protocol	7-14	
38 39 40 41		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	
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

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1 2 3 4	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
5 6 7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to $\vec{a}$ here $\vec{b}$ of the statistical analysis plan can be found, if not in the protocol	14, 15
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14, 15
10 11 12 13 14 15		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomined analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14, 15
	Methods: Monitorir	ng	and of the second se	
16 17 18 19 20	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report fructure; statement of whether it is independent from the sponsor and competing interests; and reference whether further details about its charter can be found, if not in the protocol. Alternatively, an explanation of whether it is needed	n.a.
21 22 23 24		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.
25 26 27	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously peported adverse events and other unintended effects of trial interventions or trial conduct	8
27 28 29 30 31	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.
32 33	Ethics and dissemi	nation	gines at	
33 34 35 36 37 38 39 40 41 42	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) apla oval	16
	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creations, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals, regulators)	16
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4 5 6 7 8 9	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 biolog and be studies, if applicable	n.a.
	Confidentiality	27	How personal information about potential and enrolled participants will be collected area, and maintained in order to protect confidentiality before, during, and after the trial	8
10 11 12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall transford each study site	19
13 14 15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contracts al agreements that limit such access for investigators	19
16 17 18	Ancillary and post- trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those where suffer harm from trial participation	n.a.
20 21 22 23	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 data as sharing arrangements), including any publication restrictions	16
24 25		31b	Authorship eligibility guidelines and any intended use of professional writers	n.a.
26 27 28		31c	Plans, if any, for granting public access to the full protocol, participant-level datas and statistical code	16
29 30	Appendices		ee 11,	
31 32 33	Informed consent materials	32	Model consent form and other related documentation given to participants and automotic surrogates	Supplement 3
34 35 36	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for generatic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.
<ol> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> </ol>	*It is strongly recomm Amendments to the p " <u>Attribution-NonComm</u>	nended protocol <u>mercial</u> -	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Co-NoDerivs 3.0 Unported" license.	ation on the items. ommons