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Gut-Directed Hypnotherapy Versus Standard Medical Care for Nausea in Children with Functional Nausea or Functional Dyspepsia: Protocol of a Multi-Center Randomized Trial.

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4 **Functional Nausea or Functional Dyspepsia: Protocol of a Multi-Center Randomized Trial.**
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Abstract

Introduction: The treatment of chronic functional nausea or nausea due to functional dyspepsia in children is generally symptomatic. Moreover, these disorders pose a risk for worse psychosocial and health outcomes in children. Hypnotherapy, by its ability to positively influence gastrointestinal and psychosocial functioning, may be an effective treatment for chronic nausea.

Methods and analysis: To test efficacy, this multi-center, parallel, randomized controlled, open label trial evaluates whether gut-directed hypnotherapy (HT) is superior to standard medical care (SMT) for reducing nausea. The study will be conducted at eleven academic and non-academic hospitals across the Netherlands. A total of hundred children (8-18 years), fulfilling the Rome IV criteria for chronic idiopathic nausea or functional dyspepsia with prominent nausea, will be randomly allocated (1:1) to receive HT or SMT. Children allocated to the HT group will receive six sessions of HT during three months, while children allocated to the SMT group will receive six sessions of SMT + supportive therapy during the same period. The primary outcome will be the difference in the proportion of children with at least 50% reduction of nausea, compared to baseline at twelve months follow-up. Secondary outcomes include the changes in abdominal pain, dyspeptic symptoms, quality of life, anxiety, depression, school absences, parental absence of work, health-care costs, and adequate relief of symptoms, measured directly after treatment, six and twelve months follow-up. If HT proves effective for reducing nausea, it may become a new treatment strategy to treat children with chronic functional nausea or functional dyspepsia with prominent nausea.

Ethics and dissemination: Results of the study will be publically disclosed to the public, without any restrictions, in peer-reviewed journal and international conferences. The study is approved by the Medical Research Ethics Committees United (MEC-U) in the Netherlands.

Registration details: Dutch trial registration number is NTR5814. Registered on 7 June 2016.

<http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5814>

Keywords: Hypnotherapy, Functional Nausea, Functional Dyspepsia, Children, Adolescents

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Article summary (strengths and limitations)

- First study to investigate the effectiveness of hypnotherapy on symptoms of nausea in children and adolescents, diagnosed with chronic idiopathic nausea or functional dyspepsia.
- A multicenter study with eleven participating academic and non-academic hospitals recruiting 100 children and adolescents.
- Long-term study follow-up of one year.
- Due to the nature of hypnotherapy, children, parents, and health care providers are not blinded for the received treatments.

1. Introduction

Chronic idiopathic nausea (CIN) and functional dyspepsia (FD) affect approximately 0.5% and 4.5-7.6% children worldwide (Robin et al., 2017), respectively, and are associated with substantial physical and psychosocial distress, school absences and decreased social functioning (Kovacic, 2013; Perez, 2007; Russell, 2015). Moreover, it has a considerable negative financial impact on health care (Brook et al., 2010). According to the Rome IV criteria, when no evidence of organic disease is found, the disorders are considered functional. Children meet the Rome IV criteria for CIN when they suffer from chronic nausea without abdominal pain, when symptoms are not related to meals, and not consistently associated with vomiting. Children are diagnosed with FD when they have chronic symptoms of epigastric pain/burning, symptoms of postprandial fullness, and/or early satiation (Hyams et al., 2016).

The treatment of CIN and FD with prominent nausea in pediatric patients is mostly symptomatic and not well defined. Most clinicians individualize the patient's medical treatment, including prokinetics, anti-emetics, antacids, and herbal products, according to their symptoms and associated comorbidities (Perez et al., 2007; Russell et al., 2015). The major disadvantage of this approach is that this treatment is symptomatic, and thus drugs often need to be used as long as patients suffer from nausea, which may take years (Madani, 2016; Rodriguez, 2013). Hence, there is a need for additional effective treatments for nausea in children with CIN or FD.

Several pathophysiologic mechanisms have been proposed to play a role in the etiology of CIN and FD, including delayed gastric emptying, impaired gastric motility and/or abnormal central nervous system processing of gastric stimuli through the gut-brain axis

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3 (Perez, 2007). Additionally, there are indications that psychological factors, including anxiety
4 and stress, may increase the severity of nausea through the gut-brain axis (Kellow et al.,
5 2006; Oudenhove et al., 2008).
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8 Gut-directed hypnotherapy (HT) may have the potential to reduce symptoms of
9 nausea in children with CIN or FD. HT is a form of therapy in which a therapist, by using
10 suggestions, can induce a hypnotic state in an individual to positively modify physiological,
11 cognitive, and affective processes, as well as behavior in that individual (Häuser, 2016). It has
12 been shown to be very effective in the treatment of adults and children with functional
13 abdominal pain (Miller et al., 2015; Vlieger, 2007) and children with chemotherapy-induced
14 nausea and vomiting (Richardson et al., 2007). Therefore we hypothesize that HT, by its
15 ability to influence gut motility (Whorwell, 1992), psychological well-being (Gonsalkorale,
16 2002) and visceral hypersensitivity (Lea et al., 2003; Lowén et al., 2013; Prior, 1990), might
17 alleviate symptoms of nausea in children with CIN or FD as well. To date, however, no
18 studies have examined the potential effect of HT in children with CIN or FD.
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27 The main goal of this multi-center randomized controlled trial is to evaluate the
28 effectiveness of HT in reducing symptoms of nausea in children with CIN or FD. Six sessions
29 of gut-direct HT will be compared with six sessions of SMT plus supportive therapy in 100
30 children with CIN or FD between 8 and 18 years. Additionally, we will investigate the
31 potential influence on abdominal pain, dyspeptic symptoms, quality of life, anxiety,
32 depression, school absences, parental absence of work and health-care costs. We expect
33 that HT will be more effective in reducing symptoms of nausea than standard medical care.
34 Furthermore, we expect that children receiving hypnotherapy will report more relief of
35 symptoms (e.g. less abdominal pain, less dyspeptic symptoms), better quality of life, less
36 symptoms of anxiety and depression, less absence from school, compared to children
37 receiving standard medical care. We also expect that parents of children in the
38 hypnotherapy group will report less parental absences from work and lower health care
39 costs, compared the medical care group.
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2. Methods

2.1 Trial design

The present study in children and adolescents is a multi-center randomized controlled trial (RCT). Hundred children between ages 8 and 18 years with symptoms of nausea and fulfilling the Rome IV criteria for CIN or FD, diagnosed by their pediatrician, will be enrolled in the study. After randomization, children will receive either 6 sessions of gut-directed HT during 3 months by a qualified hypnotherapist, or 6 sessions of SMT plus supportive therapy from their pediatrician during 3 months (see Figure 1). Detailed information on the HT and SMT interventions can be found under the section '2.5. Intervention'. The additional file 1 presents the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (see additional File 1).

2.2. Patient and Public Involvement

Patients and the public were not involved in the design of the RCT.

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Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure displaying the trial design and the outcome measurements. After screening for eligibility (t-1), children and parents sign the informed consent form and fill in the baseline questionnaire (t0). Children are then randomized in the hypnotherapy (HT) or standard medical care (SMT) group. Assessments take place before the start of treatment (baseline; t0), 6 weeks after the start of treatment (t1), 3 months after the start of treatment (t2), 6 months follow-up (t3) and 12 months follow-up (t4).

2.3 Recruitment

2.3.1 Recruitment procedures

Children and adolescents will be recruited in outpatient pediatric clinics of 1 academic and 10 non-academic hospitals in the Netherlands: Academic Medical Center (Amsterdam), Amphia Hospital (Breda), Maxima Medical Center (Veldhoven), Northwest Clinics (Alkmaar), Maastad Hospital (Rotterdam), Zuyderland Medical Center (Heerlen), Rijnstate Hospital, (Arnhem), Haaglanden Medical Center (Den Haag), Spaarne Hospital (Hoofddorp), Isala Clinics (Zwolle) and St. Antonius Hospital (Nieuwegein). These centers are located in both urban and rural areas throughout the Netherlands, serving an ethnically diverse pediatric population.

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2.3.2. Participant screening

All children with symptoms of nausea and fulfilling the Rome IV criteria for CIN or FD, will undergo blood laboratory testing before inclusion, including complete blood cell count, C-reactive protein, liver function tests, creatinine, total bilirubin, and for celiac screening, amylase anti-transglutaminase antibodies and IgA testing. Additionally, urinalysis and stool analysis for parasites (*Giardia Lamblia*, *Entamoeba Histolytica*) and *Helicobacter pylori* antigens will be performed. The need for additional diagnostic testing, for example endoscopy to rule out eosinophilic esophagitis or 24h pH, will be left to the discretion of the treating pediatrician or pediatric gastroenterologist. The flow of the study protocol is presented in Figure 2.

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Figure 2. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram indicating the number of participants throughout the study. After eligibility screening, children are randomized in either the hypnotherapy (HT) or standard medical care (SMT) group. Follow-up measurements take place at 6 weeks after the start of treatment (t1), 3 months after the start of treatment (t2), and 6 months follow-up (t3) and 12 months follow-up (t4).

2.4. Criteria

2.4.1. Inclusion criteria

A total sample of 100 children and adolescents with CIN or FD with symptoms of nausea will be enrolled in the study. Children and adolescents can participate in this study if they meet the following inclusion criteria:

- Age 8 to 18 years at inclusion of the study
- Diagnosis of CIN or FD, with symptoms of nausea, according to Rome IV criteria (Hyams et al., 2016)
- Sufficient knowledge of the Dutch language

2.4.2. Exclusion criteria

Children will not be enrolled in the study if they meet the following exclusion criteria:

- Concomitant organic gastrointestinal disease
- Simultaneous treatment by another health care professional for symptoms of nausea
- Previously received hypnotherapy
- Intellectual disability

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2.5. Randomization, blinding, and treatment allocation

After obtaining informed consent, children are randomly allocated, by the treating pediatricians, to one of the two treatment arms: HT, given by a qualified therapist, or SMT, meaning treatment by the child's pediatrician. A computerized random-number generator will be used to randomly allocate children on a 1:1 basis with varying block sized of 2, 4 and 6. To ensure allocation concealment, central randomization will be applied and the random allocation sequence remains concealed from pediatricians enrolling children into the study. Due to the nature of HT, it is not possible to blind the participating children and health care professionals involved in the treatment of the participants.

2.6. Intervention

2.6.1. Hypnotherapy

Individual HT consist of 6 sessions of 50-60 minutes, given over a period of 3 months by a qualified hypnotherapist. Twelve hypnotherapist affiliated to the recruiting hospitals will offer the HT to children. All hypnotherapists have years of experience in performing HT in children. The hypnotherapists will use an adapted version of our previously used HT protocol (Rutten et al., 2017; Vlieger et al., 2007). The HT protocol contains exercises focusing on normalization of the gut motility, stress reduction and ego strengthening. The hypnotherapists will be instructed to use the same scripts, but are allowed to adapt the content to the child's needs. The same protocol is used for children of all ages. However, the language used will be adjusted to the child's developmental age.

In the first session, an introduction to HT will be given to the child and parents, including an explanation of what HT is and how it may help in reducing symptoms of nausea.

Furthermore, the hypnotherapist will take a full history and children and parents are instructed to not talk about the nausea during the treatment period. The hypnotherapist will then start with a breathing exercise and introduce a progressive relaxation, in which children imagine floating on a big cloud. Positive suggestions to increase the child's belly comfort will also be provided. For instance, the child will be instructed to make hands warm and place both hands on the belly, imagining warmth spreading through their abdomen, and especially the stomach.

In the second session, the therapist will repeat the exercise on progressive relaxation.

Additionally, the therapist will introduce an exercise focusing on reduction of anxiety and

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stress, which is called 'the favorite place exercise'.

The third session focuses on ego strengthening and a new exercise will be introduced: 'the rainbow planet exercise' for children attending primary school, and 'the air balloon exercise' for children in secondary school. In the first exercise, children choose a personal need from a rainbow that contains different needs, for example a healthy stomach, courage, tranquility, or confidence.

In the fourth session, children are encouraged to release stress during the 'the beach without worries exercise' and additional ego strengthening suggestions are made.

The fifth session focuses on reduction of anxiety, stress and ego strengthening, as well as improved functioning of the digestive system. For the digestive system, children visualize a well working digestive system with food sliding through the stomach and bowel in a comfortable way.

In the sixth session, the previous sessions will be evaluated, remaining gastro-intestinal problems may be addressed and preceding exercises may be repeated, if requested by children. If no improvement has taken place, an exercise will be introduced in which the child is instructed to look inside the stomach to see 'what the stomach needs'.

After the first session, all children will receive a CD containing standard scripts of the exercises used during the sessions. The hypnotherapist will advise children to self-practice these exercises on a daily basis. Additionally, the therapist will encourage children to practice breathing exercises a few time a day.

2.6.2. Standard medical care + supportive therapy

In the SMT group, children will visit their treating pediatrician 6 times over a 3-month period. All pediatricians will be instructed to use the same protocol for treating symptoms of nausea. The protocol consists of a stepwise approach. In the first step, children and parents will be educated about CIN and FD, reassured that there is no structural organic underlying disease present, and dietary and lifestyle advices will be provided. Children will be advised to adhere to national practical guidelines for healthy eating by the Netherlands Nutrition Centre. Children will be recommended to avoid products containing caffeine, strong spices, citrus fruits, onions, fatty foods, and if applicable, to stop smoking. Additionally, the pediatrician will explore, together with children and parents, possible connections between stressful moments, emotional problems and complaints of nausea. If connections are

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3 present, the pediatrician will encourage children and parents to improve coping strategies to
4 effectively manage stress, to reduce external stressors, and to ensure an optimal
5 environment with sufficient relaxation. Children will also be encouraged to continue their
6 normal daily and sport activities and to go to school, to prevent or decrease avoidance
7 behavior.
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11 In case this does not result in adequate relief of symptoms, the pediatrician continues with
12 the second step. In the second step, proton pump inhibitors (PPI) in combination with
13 domperidone will be prescribed. If this treatment is not effective in reducing symptoms the
14 pediatrician continues with the third step, which includes the prescription of ondansetron
15 and (dis)continuation of PPIs. If again no adequate improvement occurs, in the fourth step,
16 Iberogast will be started for children >12 years. If children do not respond to Iberogast (>12
17 years) or ondansetron (<12 years), the pediatrician will continue with the fifth step and
18 prescribe erythromycin. Finally, if previous treatment did not prove to be successful in
19 reducing symptoms, cyproheptadine will be prescribed.
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22 The pediatrician will evaluate each step after two to four weeks. All dosages, except for
23 Iberogast, will be prescribed according to www.kinderformularium.nl (Dutch medical
24 guideline for pediatricians).
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27 In addition to the medical treatment, children will receive 6 half hour sessions of supportive
28 therapy given by the treating pediatrician. In these sessions, the symptom progression will
29 be discussed and patient education will be provided. Moreover, exploration of potential
30 contributing triggers (i.e. dietary product, emotional problems and stressful events) will be
31 evaluated together with children and parents. Supportive therapy is added to correct for the
32 patient-therapist time in the HT group.
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44 *2.6.3. Co-interventions*

45 After 6 sessions of HT, children visit their pediatrician to evaluate the effects of HT and, if
46 considered necessary, to receive additional medical care.
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50 **2.7. Outcomes**

51 *2.7.1. Primary outcome*

52 The primary outcome of the RCT is the proportion of patients with at least 50% reduction of
53 their symptoms of nausea compare to baseline at 12 months follow-up. Children and
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adolescents report symptoms of nausea at home by using the 7-day diary. To promote retention and complete follow-up, children and parents will be reminded on regular basis, via email and phone calls, to fill in the 7-day diary and other questionnaires.

7-day diary

The 7-day diary is used by children and adolescents to score the severity, incidence and frequency of symptoms of nausea, every day during 7 consecutive days (Rutten et al., 2014; Vlieger et al., 2007, 2012).

The *severity* of nausea is assessed by the 'nausea face' analog scale, a validated tool in the pediatric population (Baxter, 2011). Children rate their degree of nausea on a day using 6-faces: face 0 indicates no nausea and face 6 indicates nausea as bad as it can be imaged. Scores on the 'nausea face' scale are transported to a daily 0-10 score. Face 0, no nausea, is scored as 0, face 1 is scored as 2, face 2 is scored as 4, face 3 is scored as 6, face 4 is scored as 8 and face 5 is scored as 10 (Baxter et al., 2011). The 'severity of nausea' (SON) score is calculated by summing up the scores of seven days, giving a maximum of score of 70 (Rutten et al., 2017; Rutten et al., 2014; Vlieger et al., 2007, 2012).

The *incidence* nausea is assessed using the 'nausea incidence' scale (NIS), adapted from the 5-point dyspepsia Likert scale (Canan, 2011; De Luca et al., 2004). It measures the incidence of symptoms during a day, where score 0 for no nausea, score 1 for 1-2 times a day, score 2 for 3-5 times a day, score 3 for intermittent complaints and score 4 for complaints were always present. The total sum of the scores of seven days indicates the severity of the nausea during a week, as experienced by the child. The maximum total score is 28 (Rutten et al., 2017; Rutten et al., 2014; Vlieger et al., 2007, 2012).

The *frequency* of symptoms of nausea is recorded in minutes/hours per day and is scored by children as 0 when there was no nausea, 1 if children had <10 minutes of nausea, 2 for 10-30 minutes of nausea, 3 for 30 minutes-2 hours of nausea, 4 for 2-4 hours of nausea and 5 if the nausea lasts >4 hours a day. The 'nausea frequency score' (NFS) is calculated by summing the scores of the seven days, with a maximum of 35 (Rutten et al., 2014; Vlieger et al., 2007, 2012).

2.7.2. Secondary outcomes

In addition to the primary outcomes, the present study investigates secondary outcomes,

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3 including abdominal pain, dyspeptic symptoms, health related quality of life, anxiety,
4 depression, school absences, parental absence of work and health-care costs. Secondary
5 outcomes are measured at 6 weeks and 3 months after treatment, and at 6 and 12 months
6 follow-up after the end of treatment (Figure 1).
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10 11 *Abdominal pain*

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13 A 7-day diary is used to assess the severity and frequency of abdominal pain, every day
14 during 7 consecutive days. It comprises of two subscales: the abdominal pain intensity
15 subscale (APIS) and abdominal pain frequency subscale (APFS). The APIS will be scored using
16 an affective facial scale ranging with face 0 indicating 'no pain at all' to face 5 indicating 'the
17 most severe pain'. No abdominal pain is scored as 0, faces 1 - 2 are scored as 1, faces 3 - 4
18 are scored as 2 and face 5 is scored as 3. The scores of seven days are summed up, with a
19 maximum score of 21 (Rutten et al., 2017; Rutten et al., 2014; Vlieger et al., 2007, 2012). The
20 APFS is recorded in minutes/hours of abdominal pain per day, with score 0 indicating no
21 pain, score 1 if children had <10 minutes of pain, 2 for 10-30 minutes of pain, 3 for 30
22 minutes-2 hours of pain, 4 for 2-4 hours of pain and 5 >4 hours of pain. The scores the APFS
23 are summed up, giving a pain frequency score of maximum 35 (Rutten et al., 2017; Rutten et
24 al., 2014; Vlieger et al., 2007, 2012).
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34 *Dyspeptic symptoms*

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36 Severity and incidence of dyspeptic symptoms is measured using the 5-point dyspepsia
37 Likert scale, previously used in the pediatric population (Canan, 2011; De Luca, 2004). The
38 dyspepsia Likert scale consists of 8 gastrointestinal dyspeptic symptoms: epigastric pain,
39 upper abdominal discomfort, retrosternal pyrosis, sour-bitter taste, halitosis, belching,
40 nausea, and early satiety. Children score the *severity* of each symptoms during the previous
41 two weeks on a 5-point Likert scale: score 1 'no complaints at all', score 2 'little complaints',
42 score 3 'moderate complaints', score 4 'quite a lot of complaints' and 5 'serious complaints'
43 (Canan et al., 2011). A higher sum score indicates more severe dyspeptic complaints (SDC
44 score), with a maximum of 40.
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51 Children report on the *incidence* of each of the symptoms during the previous two weeks by
52 scoring: 1 'no complaints', 2 '1-2 times a week', 3 '3-5 times a week', 4 'intermittent
53 complaints' and 5 'complains were always present' (Canan et al., 2011). The dyspepsia
54 severity score (DSS) is calculated by summing up the scores, giving a maximum value of 40.
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Health related quality of life

The KIDSCREEN-52 questionnaire measures health related quality of life (QoL) in children and adolescents. The questionnaire has been shown a valid tool in the Dutch pediatric population (Ravens-Sieberer et al., 2008; The Kidscreen Group Europe, 2006). The KIDSCREEN-52 consists of items on ten dimensions related to QoL on a 5-point Likert scale: moods and emotions, self-perception, relations with parents and home life, autonomy, physical well-being, psychological well-being, school environment, social support and peers, social acceptance (bullying) and financial resources. For each individual dimension, Rasch scores are computed from the individual items. These are then transformed into T-values: higher T-values indicate a better health related QoL and well-being.

Anxiety and depression

Anxiety and depression are evaluated using the Revised Anxiety and Depression Scale-short version (RCADS-25). This questionnaire has been previously validated in the Dutch pediatric population (Muris, 2002). The RCADS-25 consists of five subscales measuring symptoms of generalized anxiety disorders, separation anxiety disorder, social phobia, panic disorder and major depressive disorder. Each subscale contains five items and scales range from 0 (never) to 3 (always). The total score on anxiety or depression is the sum of the items measuring symptoms of anxiety and depressive symptoms, respectively. Higher scores indicate more symptoms of anxiety or depression.

Cost effectiveness/cost utility

The Health Utility Index Mark 3 (HUI) will be used in the cost-utility and cost-effectiveness analysis. The HUI-3 is a multi-attribute utility measure of health status in children as reported by parents. Proxy measurements of parents for health status of children are justifiable, as some children may be too young to provide reliable and valid information about their own health status (Eiser & Morse, 2001; Feeny et al., 2002; Tarride et al., 2010). The questionnaire consists of eight dimensions of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain with 5 or 6 levels per attribute, which scales varying from highly impaired to normal. Health utilities of 1 indicate perfect health, whereas 0 indicates death. The Quality adjusted life years (QALY) will be calculated by multiplying the sum of the utility of health states by the time in between measurements.

Work absenteeism by parents and school absenteeism by children

An adapted version of the Dutch Health and Labor Questionnaire (HLQ) will be used to

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3 measure work absenteeism by parents, school absenteeism by children, and indirect costs of
4 health care utilization (Van Roijen, 1996). This adapted version contains three items. Parents
5 indicate whether their child has been absent from school due to complaints of nausea, and if
6 yes, the amount of hours per week. For work absenteeism by parents, parents indicate the
7 number of hours they worked less on average because of their child's symptoms of nausea.
8 For the indirect costs of health care utilization, parents indicate additional costs they had
9 due to symptoms of nausea of their child over the past four weeks.
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14 *Somatization*

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16 The Children's Somatization Inventory (CSI) measures the extent to which children and
17 adolescents experience somatic symptoms. The questionnaire has been shown a valid and
18 reliable self-report instrument in the pediatric population (Meesters, 2003). The CSI consists
19 of 35 items and on a 5-point Likert scale (0 = not at all to 4 = a whole lot) and children rate
20 the extent to which they experienced somatic symptoms in the previous two weeks. The
21 total score is calculated by summing up the 35 items, with higher scores indicating higher
22 intensity of somatic complaints experienced by the child.
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28 In order to calculate a separate CSI-score for non-gastrointestinal (GI) symptoms, 7 items on
29 GI-symptoms (nausea, constipation, diarrhea, epigastric and abdominal pain, vomiting and
30 bloating) are left out. The total score of somatic symptoms without GI-symptoms is
31 calculated by summing up the scores of non-GI symptoms, with higher scores reflecting
32 higher intensity of non-GI somatic complaints.
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37 *Adequate relief*

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39 Parents and children will be asked whether adequate relief of symptoms of nausea has
40 occurred, using a dichotomous scale (yes/no). Adequate relief has been previously used as
41 an endpoint in clinical trials assessing hypnotherapy in children and adolescents (Rutten et
42 al., 2017) and has been shown a valid outcome measure for functional gastrointestinal
43 disorders (Mangel et al., 1998).
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49 **2.8. Sample size calculation**

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51 The primary outcome of the RCT is the proportion of patients with at least 50% reduction of
52 their symptoms of nausea compare to baseline at 12 months follow-up. Based on our pilot
53 study (Vlieger, A. M. "A pilot-study of hypnotherapy as a treatment for functional nausea in
54 children") and the success percentages in studies using hypnotherapy in adults with
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3 functional dyspepsia (Calvert, 2002) and in pediatric cancer patients (Richardson et al.,
4 2007), we expect that 80% of the children in the hypnotherapy group will have >50%
5 reduction of their symptoms of nausea after one year. In the standard medical care group,
6 we anticipate that 50% of the children will have >50% reduction of their symptoms of
7 nausea after one year. Based on these expected proportions, 45 children per group will be
8 needed to achieve a power of 80% with a one-sided significance level of 5%. Accounting for
9 a 10% dropout, 100 children will be included in this study. If a child is prematurely
10 withdrawn from the study, he/she will not be replaced; data will be analyzed according to
11 the intention to treat analysis.
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19 **2.9. Statistical analysis**

20 *2.9.1. Primary outcome*

21 Outcomes will be analyzed according to the intention to treat (ITT) analysis. For the primary
22 outcome, the Chi-square test will be used to compare the proportions of patients with >50%
23 reduction of symptoms of nausea (i.e. severity, incidence and frequency of nausea) after 12
24 months follow-up between the two groups (HT versus SMT). For all analysis, the significance
25 level for statistical analysis is set at $\alpha = 0.05$. Multiple imputation will be applied to deal with
26 cases of missing data.
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34 *2.9.2. Secondary outcomes*

35 For the secondary outcomes, including the potential influence on abdominal pain, dyspeptic
36 symptoms, health related quality of life, anxiety, depression, work absenteeism by parents,
37 school absenteeism by children, somatization and adequate relief, the Student's *t*-test will
38 be used for means of normally distributed data, the Mann–Whitney U test for
39 nonparametric data and the Chi-square test to compare proportions. To calculate the cost-
40 effectiveness, cost-utility and cost-effectiveness ratios will be calculated for the extra costs
41 per child with >50% reduction of symptoms of nausea and the extra costs per QALY.
42 As secondary analysis, the proportion of patients with >50% reduction of their nausea
43 (severity, incidence and frequency) after treatment, 6 months and 12 months follow up will
44 be compared between groups using multivariate logistic regression correcting for age and
45 center.
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3. Amendments

Prior to implementation, amendments will be examined and approved by the METC. The sponsor will only record non-substantial amendments.

4. Data monitoring

Hypnotherapy is usually well tolerated in children, without significant side effects. In our previous trials only a minority of children reported some dizziness, mostly during or directly after the end of the first session (Rutten et al., 2014; Vlieger et al., 2007). In case children experience dizziness, they will be advised to execute the remaining sessions in a sitting position instead of a supine position. Children assigned to the SMT group will receive standard medical treatment, including drugs that have been either registered for children, or of which side effects are limited and well known. For these reasons, no Data Monitoring Safety Board will be established.

Study auditing will be accomplished by periodic visits to the participating centers, and by email and telephone contact with local investigators, to ensure the study protocol is being complied with and to discuss any problems that might have arisen.

5. Potential harms

In accordance to the legal requirements in the Netherlands (article 10, subsection 1, WMO), the investigator will inform the subjects and the reviewing accredited METC if harmful events occur. When there are indications that the disadvantage of participation may be significantly greater than was described in the research proposal, the study will be suspended pending further review by the accredited METC. However, the study will not be suspended if it would jeopardize participating children's health.

6. Ancillary and post-trial care

In accordance with Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 200th, the sponsor has liability insurance, which provides cover for potential damage to children caused by the study.

7. Data storage

The related information on paper, including 7-day diaries, will be securely stored in a locked file cabinet with limited access. Online questionnaire data will be securely stored using the University's password-protected access systems. Only the main researchers will be given full

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access to the questionnaire data. All records that contain names will be saved in one file, which will be password protected and only accessible to the main researchers.

8. Dissemination policy

The researchers will communicate trial results to the public, health care providers, and other relevant groups via reports, and by publishing in peer-reviewed journals. Negative as well as positive results will be published. The results will be shared with participating children and parents after completion of the trial. All authors who provided substantial contributions to the conduct, interpretation, and reporting of the results will be granted authorship on the final trial report.

9. Discussion and conclusion

Chronic nausea is a highly disabling symptom for children with CIN or FD, and poses a risk for negative health outcomes and decreased psychosocial functioning (Kovacic et al., 2013; Perez & Youssef, 2007; Russell et al., 2015). To date large randomized placebo controlled trials evaluating the effect of any drug in children with either CIN or FD are lacking. Current medical treatment aiming to relieve nausea is experienced based, however these treatments are symptomatic and often used for months or years. For these reasons, new effective treatment options to reduce nausea in children with CIN or FD are warranted.

There are indications that HT can decrease symptoms of functional nausea and dyspepsia in adults (Calvert et al., 2002), and functional abdominal pain (FAP) (Vlieger et al., 2007) and chemotherapy induced nausea in children (Richardson, 2007). Calvert et al. (2002) found that adult patients with FD receiving 12 sessions of HT had significantly less dyspeptic symptoms (59%, N=26) compared to patients receiving medical treatment (33%, N=29) ($p=0.02$). These beneficial effects were maintained for more than a year: 56 weeks after the first treatment, 73% of the patients in the HT group reported symptom improvement compared to 43% in the medical treatment group ($p<0.01$). In children with FAP, Vlieger (2007) found that HT was highly superior compared to standard medical care to reduce abdominal pain. At one year follow-up, 85% of the children in the HT group (N=26) were in clinical remission compared to 85% of the children in the SMT group (N=24) ($p<0.001$). Additionally, a systematic review including six RCTs evaluating the effectiveness of

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3 hypnotherapy to reduce chemotherapy-induced nausea found hypnotherapy was most
4 effective when compared with standard medical care to reduce complaints ($D=0.99$)
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6 (Richardson, 2007).
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10 The present study is the first study to investigate the effectiveness of HT on symptoms of
11 nausea in children and adolescents diagnosed with CIN or FD, according to the Rome IV
12 criteria. If shown effective, it may provide an additional treatment option for children with
13 CIN or FD.
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16 The study has several strengths. The first strength is that pediatricians from eleven different
17 hospitals throughout the Netherlands will recruit all children and adolescents. The hospitals,
18 both an academic center and teaching hospitals, serve an ethnic and socio-economic diverse
19 population of children and adolescents. This recruitment method has two advantages: first,
20 it may reduce response bias to the intervention. It has previously been reported that
21 patients from primary and secondary level care may have different responses to treatment
22 (Veldhuyzen van Zanten et al., 1999). All children included in the present study receive
23 secondary level care. The second advantage is that the multicenter design of the study will
24 increase generalizability of the trial outcomes.
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27 Another strength of the study is the long-term follow up of one year, which allows us to
28 properly compare the potential effectiveness of HT with SMT. It has been known that the
29 severity of functional gastrointestinal symptoms in children varies over time (Miele et al.,
30 2004) and a continuous improvement in symptoms is often reported in children receiving
31 hypnotherapy (Vlieger et al., 2007).
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34 This study also has several limitations. The first limitation is that children, parents,
35 investigators and health care providers are not blinded for the received treatments, which is
36 not possible due the nature of HT. Several solutions will be applied to limit the risk of bias.
37 First, to minimize performance bias, pediatricians and hypnotherapists will follow treatment
38 guidelines to prevent any use of additional or alternative forms of care during the study
39 period that may influence treatment outcomes. Second, to reduce the risk of detection bias,
40 children and adolescents use reliable outcome measures and record symptoms themselves
41 at home. Moreover, children and adolescents record symptoms of nausea for seven
42 consecutive days, which corrects for individual variability of symptoms over time. Third, the
43 endpoints of the study will be preregistered and the data analyst will be blinded during the
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analyses of data.

The second limitation is that the SMT provided by pediatricians in this study may not reflect usual clinical practice. In the present study, children and adolescents receive longer and more intensive medical therapy from their pediatrician compared to the real medical practice situation. However, previous studies indicate that patient-provider interactions can largely influence gastrointestinal treatment outcomes (Dossett et al., 2015). Therefore, it is important to control for the time spent per patient in the SMT group.

If the results of this study show that HT given by a therapist is comparable or slightly more effective than medical treatment provided by pediatricians, HT may become a new treatment strategy to help children with CIN or FD. Furthermore, as HT is presumably less costly than treatments by a specialist it may also decrease health care costs.

Abbreviations

APIS: Abdominal Pain Intensity Subscale; **APFS:** abdominal pain frequency subscale; **CIN:** Chronic Idiopathic Nausea; **CSI:** Children's Somatization Inventory; **FAP:** Functional Abdominal Pain; **FD:** Functional Dyspepsia; **FGID:** Functional Gastrointestinal Disorders; **GI:** gastrointestinal; **HLQ:** Health and Labor Questionnaire; **HT:** Hypnotherapy; **HUI:** Health Utility Index Mark 3; **ITT:** Intention to Treat Analysis; **MEC-U:** Medical Research Ethics Committees United; **NIS:** Nausea Incidence Scale; **NFS:** Nausea Frequency Score; **PPI:** Proton Pump Inhibitors; **QALY:** Quality Adjusted Life Years; **QoL:** Health related Quality of Life; **RCADS-25:** Revised Anxiety and Depression Scale-short version; **RCT:** Randomized Controlled Trial; **REC:** Research Ethical Committees; **SMT:** Standard Medical Care plus supportive therapy; **SON:** Severity Of Nausea; **WMO:** Medical Research Involving Human Subjects Act

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None

Competing interests

The authors declare no competing interests.

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Author contributions

AV is the principle investigator, designed the study, wrote the protocol, supervised the trial and supervised writing the manuscript. PB provided adjustments to the protocol, drafted the manuscript and coordinated the trial. MB critically revised the protocol, supervised the trial and supervised writing the manuscript. All other authors participated in patient recruitment and/or treatment, read and approved the manuscript.

Trial status

Recruitment started in September 2016 and is ongoing. In October 2016, the first participant enrolled. Currently, 92 children are participating in the study (18 of them have completed the study protocol).

Ethics approval and consent to participate

This RCT was approved by the Medical Research Ethics Committees United (MEC-U) in Nieuwegein, the Netherlands (file number: NL51167.100.15). The study will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO) and conferring to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). The study will follow the conduct code concerning resistance in minors who participate in clinical trials as defined by the Dutch Pediatric Society. Informed consent will be asked from parents/guardians of children <12 years of age. In children and adolescents ≥ 12 years of age informed consent will be asked from the parents-guardians and the children and adolescents. In the event of amendments of the protocol, relevant research ethical committees (RECs) will be informed. Results of the study will be publically disclosed in a peer-reviewed journal, without any restrictions; both positive as well as negative results will be published.

5 peer reviewers suggested

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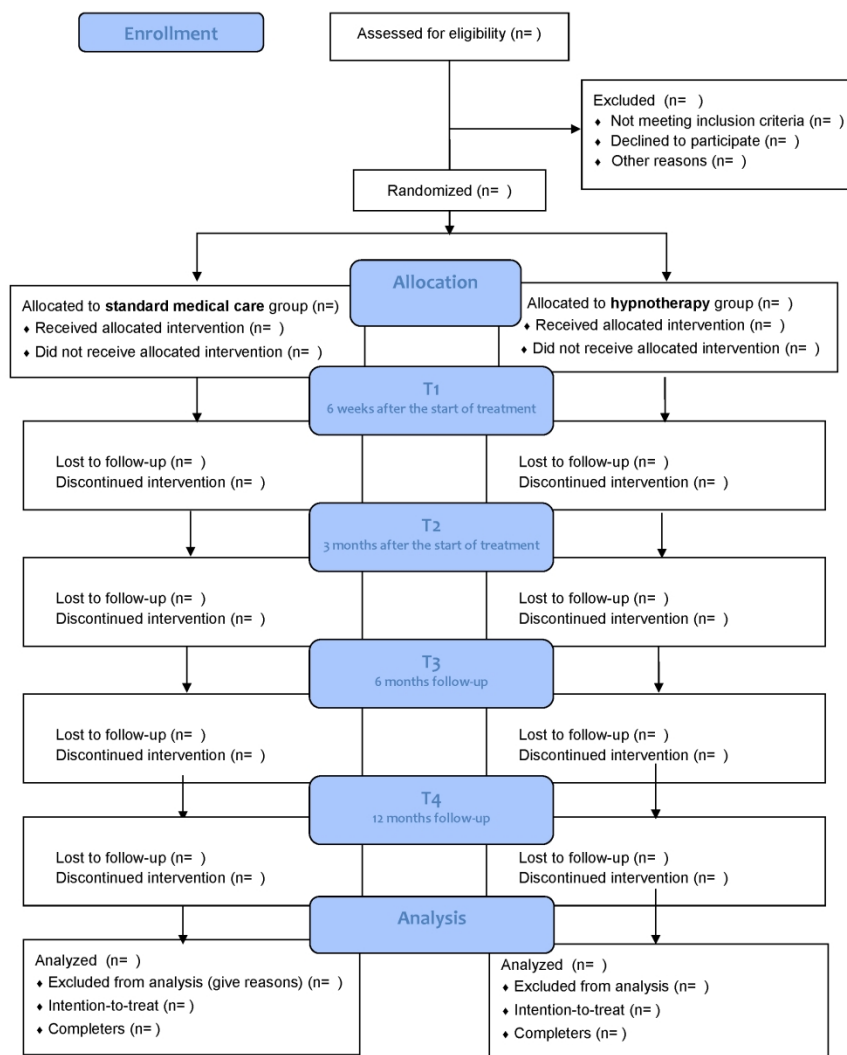
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TIMEPOINT	Enrolment	Allocation	During treatment		Follow-up	
	Before treatment (t-1)	Start of treatment (t0)	6 weeks after the start of treatment (t1)	3 months after the start of treatment (t2)	6 months follow-up (t3)	12 months follow-up (t4)
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization	X					
INTERVENTIONS:						
Hypnotherapy group (HT)		←————→				
Standard medical care group (SMT)		←————→				
ASSESSMENTS:						
Nausea and abdominal pain	X		X	X	X	X
Dyspeptic symptoms		X		X	X	X
Health related quality of life		X		X	X	X
Anxiety and Depression		X		X	X	X
Cost effectiveness/cost utility		X		X	X	X
Work absenteeism by parents and school absenteeism by children		X		X	X	X
Somatization		X		X	X	X
Adequate relief					X	X

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure displaying the trial design and the outcome measurements. After screening for eligibility (t-1), children and parents sign the informed consent form and fill in the baseline questionnaire (t0). Children are then randomized in the hypnotherapy (HT) or standard medical care (SMT) group. Assessments take place before the start of treatment (baseline; t0), 6 weeks after the start of treatment (t1), 3 months after the start of treatment (t2), 6 months follow-up (t3) and 12 months follow-up (t4).

215x279mm (300 x 300 DPI)



45 Figure 2. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram indicating the number of
46 participants throughout the study. After eligibility screening, children are randomized in either the
47 hypnotherapy (HT) or standard medical care (SMT) group. Follow-up measurements take place at 6 weeks
48 after the start of treatment (t₁), 3 months after the start of treatment (t₂), and 6 months follow-up (t₃) and
49 12 months follow-up (t₄).

50 215x279mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3-14
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 18
Roles and	#5b	Name and contact information for the trial sponsor	18

1	responsibilities:			
2	sponsor contact			
3	information			
4				
5				
6	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	18
7	responsibilities:		collection, management, analysis, and interpretation of	
8	sponsor and funder		data; writing of the report; and the decision to submit the	
9			report for publication, including whether they will have	
10			ultimate authority over any of these activities	
11				
12				
13				
14	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	NA
15	responsibilities:		centre, steering committee, endpoint adjudication	
16	committees		committee, data management team, and other individuals or	
17			groups overseeing the trial, if applicable (see Item 21a for	
18			data monitoring committee)	
19				
20				
21				
22				
23	Background and	#6a	Description of research question and justification for	3, 4
24	rationale		undertaking the trial, including summary of relevant studies	
25			(published and unpublished) examining benefits and harms	
26			for each intervention	
27				
28				
29				
30	Background and	#6b	Explanation for choice of comparators	5
31	rationale: choice of			
32	comparators			
33				
34				
35	Objectives	#7	Specific objectives or hypotheses	4
36				
37				
38	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
39			group, crossover, factorial, single group), allocation ratio,	
40			and framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	Study setting	#9	Description of study settings (eg, community clinic,	5
46			academic hospital) and list of countries where data will be	
47			collected. Reference to where list of study sites can be	
48			obtained	
49				
50				
51				
52	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6
53			eligibility criteria for study centres and individuals who will	
54			perform the interventions (eg, surgeons, psychotherapists)	
55				
56				
57				
58	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-9
59				
60				

1	description		replication, including how and when they will be administered	
2				
3				
4	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9, 15
5	modifications			
6				
7				
8				
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10				
11	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
12	adherence			
13				
14				
15				
16				
17	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
18	concomitant care			
19				
20				
21	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	9-13
22				
23				
24				
25				
26				
27				
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30				
31				
32	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)	5
33				
34				
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39				
40	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
41				
42				
43				
44				
45				
46				
47	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
48				
49				
50				
51	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign	6-7
52				
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1			interventions	
2				
3	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6-7
4	concealment		central telephone; sequentially numbered, opaque, sealed	
5	mechanism		envelopes), describing any steps to conceal the sequence	
6			until interventions are assigned	
7				
8				
9				
10	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	6-7
11	implementation		participants, and who will assign participants to	
12			interventions	
13				
14				
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6-7
16			trial participants, care providers, outcome assessors, data	
17			analysts), and how	
18				
19				
20				
21	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
22	emergency		permissible, and procedure for revealing a participant's	
23	unblinding		allocated intervention during the trial	
24				
25				
26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	9-13
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
33				
34				
35				
36				
37				
38	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	9
39	retention		up, including list of any outcome data to be collected for	
40			participants who discontinue or deviate from intervention	
41			protocols	
42				
43				
44				
45	Data management	#19	Plans for data entry, coding, security, and storage, including	15
46			any related processes to promote data quality (eg, double	
47			data entry; range checks for data values). Reference to	
48			where details of data management procedures can be	
49			found, if not in the protocol	
50				
51				
52				
53				
54	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	14-15
55			outcomes. Reference to where other details of the statistical	
56			analysis plan can be found, if not in the protocol	
57				
58				
59				
60				

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	NA
2	analyses		adjusted analyses)	
3				
4				
5	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	14
6	population and		adherence (eg, as randomised analysis), and any statistical	
7	missing data		methods to handle missing data (eg, multiple imputation)	
8				
9				
10	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15
11	formal committee		of its role and reporting structure; statement of whether it is	
12			independent from the sponsor and competing interests; and	
13			reference to where further details about its charter can be	
14			found, if not in the protocol. Alternatively, an explanation of	
15			why a DMC is not needed	
16				
17				
18				
19				
20	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	NA
21	interim analysis		including who will have access to these interim results and	
22			make the final decision to terminate the trial	
23				
24				
25				
26	Harms	#22	Plans for collecting, assessing, reporting, and managing	15
27			solicited and spontaneously reported adverse events and	
28			other unintended effects of trial interventions or trial conduct	
29				
30				
31				
32	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	15
33			and whether the process will be independent from	
34			investigators and the sponsor	
35				
36				
37	Research ethics	#24	Plans for seeking research ethics committee / institutional	P1
38	approval		review board (REC / IRB) approval	
39				
40				
41	Protocol	#25	Plans for communicating important protocol modifications	14
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
45				
46				
47				
48	Consent or assent	#26a	Who will obtain informed consent or assent from potential	19
49			trial participants or authorised surrogates, and how (see	
50			Item 32)	
51				
52				
53				
54	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
55	ancillary studies		participant data and biological specimens in ancillary	
56			studies, if applicable	
57				
58				
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60				

1	Confidentiality	#27	How personal information about potential and enrolled	15
2			participants will be collected, shared, and maintained in	
3			order to protect confidentiality before, during, and after the	
4			trial	
5				
6				
7				
8	Declaration of	#28	Financial and other competing interests for principal	18
9	interests		investigators for the overall trial and each study site	
10				
11				
12	Data access	#29	Statement of who will have access to the final trial dataset,	15
13			and disclosure of contractual agreements that limit such	
14			access for investigators	
15				
16				
17	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	15
18	trial care		compensation to those who suffer harm from trial	
19			participation	
20				
21				
22				
23	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	16
24	trial results		results to participants, healthcare professionals, the public,	
25			and other relevant groups (eg, via publication, reporting in	
26			results databases, or other data sharing arrangements),	
27			including any publication restrictions	
28				
29				
30				
31				
32	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	NA
33	authorship		professional writers	
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	NA
37	reproducible		participant-level dataset, and statistical code	
38	research			
39				
40				
41	Informed consent	#32	Model consent form and other related documentation given	NA
42	materials		to participants and authorised surrogates	
43				
44				
45	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA
46			biological specimens for genetic or molecular analysis in the	
47			current trial and for future use in ancillary studies, if	
48			applicable	
49				
50				
51				

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BMJ Open

Gut-Directed Hypnotherapy Versus Standard Medical Care for Nausea in Children with Functional Nausea or Functional Dyspepsia: Protocol of a Multi-Center Randomized Trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024903.R1
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Date Submitted by the Author:	21-Nov-2018
Complete List of Authors:	Browne, Pamela; Amsterdam UMC, Department of Pediatric Gastroenterology and Nutrition den Hollander, Bibiche; Amsterdam UMC, Department of Pediatric Gastroenterology and Nutrition Speksnijder, Esther; Amsterdam UMC, Department of Pediatric Gastroenterology and Nutrition van Wering, Herbert; Amphia Ziekenhuis, Department of Pediatrics Tjon a ten, Walther; Maxima Medical Center, Department of Pediatrics George, Elvira; Northwest Clinics, Department of Pediatrics Groeneweg, Michael; Maasstad Ziekenhuis, Department of Pediatrics Bevers, Nanja; Zuyderland Medical Center, Department of Pediatrics Wessels, Margreet; Rijnstate Hospital, Department of Pediatrics van den Berg, Maartje; Haaglanden Medical Center, Department of Pediatrics Goede, Joery; Spaarne Hospital, Department of Pediatrics Teklenburg, Sarah; Isala Clinics, Department of Pediatrics Frankenhuis, Carla; Amsterdam UMC, Department of Pediatric Gastroenterology and Nutrition Benninga, Marc; Amsterdam UMC, Department of Pediatric Gastroenterology and Nutrition Vlieger, Arine; St. Antonius Hospital, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Hypnotherapy, Functional Nausea, Functional Dyspepsia, Children, Adolescents

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Manuscripts

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3 1 **Gut-Directed Hypnotherapy Versus Standard Medical Care for Nausea in Children with**
4 **Functional Nausea or Functional Dyspepsia: Protocol of a Multi-Center Randomized Trial.**
5 2
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7 3

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1
2
3 31 **Abstract**

4
5 32 *Introduction:* The treatment of chronic functional nausea or nausea due to functional
6
7 33 dyspepsia in children is generally symptomatic. Moreover, these disorders pose a risk for
8
9 34 worse psychosocial and health outcomes in children. Hypnotherapy, by its ability to
10
11 35 positively influence gastrointestinal and psychosocial functioning, may be an effective
12
13 36 treatment for chronic nausea.

14 37 *Methods and analysis:* To test efficacy, this multi-center, parallel, randomized controlled,
15
16 38 open label trial evaluates whether gut-directed hypnotherapy (HT) is superior to standard
17
18 39 medical care (SMT) for reducing nausea. The study will be conducted at eleven academic and
19
20 40 non-academic hospitals across the Netherlands. A total of hundred children (8-18 years),
21
22 41 fulfilling the Rome IV criteria for chronic idiopathic nausea or functional dyspepsia with
23
24 42 prominent nausea, will be randomly allocated (1:1) to receive HT or SMT. Children allocated
25
26 43 to the HT group will receive six sessions of HT during three months, while children allocated
27
28 44 to the SMT group will receive six sessions of SMT + supportive therapy during the same
29
30 45 period. The primary outcome will be the difference in the proportion of children with at
31
32 46 least 50% reduction of nausea, compared to baseline at twelve months follow-up. Secondary
33
34 47 outcomes include the changes in abdominal pain, dyspeptic symptoms, quality of life,
35
36 48 anxiety, depression, school absences, parental absence of work, health-care costs, and
37
38 49 adequate relief of symptoms, measured directly after treatment, six and twelve months
39
40 50 follow-up. If HT proves effective for reducing nausea, it may become a new treatment
41
42 51 strategy to treat children with chronic functional nausea or functional dyspepsia with
43
44 52 prominent nausea.

45 53 *Ethics and dissemination:* Results of the study will be publically disclosed to the public,
46
47 54 without any restrictions, in peer-reviewed journal and international conferences. The study
48
49 55 is approved by the Medical Research Ethics Committees United (MEC-U) in the Netherlands.

50
51 56
52 57 **Registration details:** Dutch trial registration number is NTR5814. Registered on 7 June 2016.

53 58 <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5814>

54 59 **Keywords:** Hypnotherapy, Functional Nausea, Functional Dyspepsia, Children, Adolescents

55 60 **Words:** 5972

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1
2
3 **62 Article summary (strengths and limitations)**

- 4
5 **63** - First study to investigate the effectiveness of hypnotherapy on symptoms of nausea in
6
7 **64** children and adolescents, diagnosed with chronic idiopathic nausea or functional dyspepsia.
8
9 **65** - A multicenter study with eleven participating academic and non-academic hospitals
10
11 **66** recruiting 100 children and adolescents.
12
13 **67** - Long-term study follow-up of one year.
14
15 **68** - Due to the nature of hypnotherapy, children, parents, and health care providers are not
16
17 **69** blinded for the received treatments.

18
19 **70 1. Introduction**

20
21 **71** Chronic idiopathic nausea (CIN) and functional dyspepsia (FD) affect approximately 0.5% and
22
23 **72** 4.5-7.6% children worldwide [1], respectively, and are associated with substantial physical
24
25 **73** and psychosocial distress, school absences and decreased social functioning [2-4]. Moreover,
26
27 **74** it has a considerable negative financial impact on health care [5]. According to the Rome IV
28
29 **75** criteria, when no evidence of organic disease is found, the disorders are considered
30
31 **76** functional. Children meet the Rome IV criteria for CIN when they suffer from chronic nausea
32
33 **77** without abdominal pain, when symptoms are not related to meals, and not consistently
34
35 **78** associated with vomiting. Children are diagnosed with FD when they have chronic symptoms
36
37 **79** of epigastric pain/burning, symptoms of postprandial fullness, and/or early satiation [6].

38
39 **80** The treatment of CIN and FD with prominent nausea in pediatric patients is mostly
40
41 **81** symptomatic and not well defined. Most clinicians individualize the patient's medical
42
43 **82** treatment, including prokinetics, anti-emetics, antacids, and herbal products, according to
44
45 **83** their symptoms and associated comorbidities [3, 4]. The major disadvantage of this
46
47 **84** approach is that this treatment is symptomatic, and thus drugs often need to be used as
48
49 **85** long as patients suffer from nausea, which may take years [7, 8]. Hence, there is a need for
50
51 **86** additional effective treatments for nausea in children with CIN or FD.

52
53 **87** Several pathophysiologic mechanisms have been proposed to play a role in the
54
55 **88** etiology of CIN and FD, including delayed gastric emptying, impaired gastric motility and/or
56
57 **89** abnormal central nervous system processing of gastric stimuli through the gut-brain axis [3].
58
59 **90** Additionally, there are indications that psychological factors, including anxiety and stress,
60
91 may increase the severity of nausea through the gut-brain axis [9, 10].

92 Gut-directed hypnotherapy (HT) may have the potential to reduce symptoms of

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3 93 nausea in children with CIN or FD. HT is a form of therapy in which a therapist, by using
4
5 94 suggestions, can induce a hypnotic state in an individual to positively modify physiological,
6
7 95 cognitive, and affective processes, as well as behavior in that individual [11]. It has been
8
9 96 shown to be very effective in the treatment of adults and children with functional abdominal
10
11 97 pain [12, 13] and children with chemotherapy-induced nausea and vomiting [14]. Therefore
12
13 98 we hypothesize that HT, by its ability to influence gut motility [15], psychological well-being
14
15 99 [16] and visceral hypersensitivity [17-19], might alleviate symptoms of nausea in children
16
17 100 with CIN or FD as well. To date, however, no studies have examined the potential effect of
18
19 101 HT in children with CIN or FD.

20 102 The main goal of this multi-center randomized controlled trial is to evaluate the
21
22 103 effectiveness of HT in reducing symptoms of nausea in children with CIN or FD. Six sessions
23
24 104 of gut-direct HT will be compared with six sessions of SMT plus supportive therapy in 100
25
26 105 children with CIN or FD between 8 and 18 years. Additionally, we will investigate the
27
28 106 potential influence on abdominal pain, dyspeptic symptoms, quality of life, anxiety,
29
30 107 depression, school absences, parental absence of work and health-care costs. We expect
31
32 108 that HT will be more effective in reducing symptoms of nausea than standard medical care.
33
34 109 Furthermore, we expect that children receiving hypnotherapy will report more relief of
35
36 110 symptoms (e.g. less abdominal pain, less dyspeptic symptoms), better quality of life, less
37
38 111 symptoms of anxiety and depression, less absence from school, compared to children
39
40 112 receiving standard medical care. We also expect that parents of children in the
41
42 113 hypnotherapy group will report less parental absences from work and lower health care
43
44 114 costs, compared the medical care group.

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124 **2. Methods**

125 **2.1 Trial design**

126 The present study in children and adolescents is a multi-center randomized controlled trial
127 (RCT). Hundred children between ages 8 and 18 years with symptoms of nausea and fulfilling
128 the Rome IV criteria for CIN or FD, diagnosed by their pediatrician, will be enrolled in the
129 study. After randomization, children will receive either 6 sessions of gut-directed HT during 3
130 months by a qualified hypnotherapist, or 6 sessions of SMT plus supportive therapy from
131 their pediatrician during 3 months (see Figure 1). Detailed information on the HT and SMT
132 interventions can be found under the section '2.5. Intervention'. The additional file 1
133 presents the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)
134 checklist (see additional File 1).

135 **2.2. Patient and Public Involvement**

136 Patients and the public were not involved in the design of the RCT.

137 **2.3 Recruitment**

138 *2.3.1 Recruitment procedures*

139 Children and adolescents will be recruited in outpatient pediatric clinics of 1 academic and
140 10 non-academic hospitals in the Netherlands: Academic Medical Center (Amsterdam),
141 Amphia Hospital (Breda), Maxima Medical Center (Veldhoven), Northwest Clinics (Alkmaar),
142 Maastad Hospital (Rotterdam), Zuyderland Medical Center (Heerlen), Rijnstate Hospital,
143 (Arnhem), Haaglanden Medical Center (Den Haag), Spaarne Hospital (Hoofddorp), Isala
144 Clinics (Zwolle) and St. Antonius Hospital (Nieuwegein). These centers are located in both
145 urban and rural areas throughout the Netherlands, serving an ethnically diverse pediatric
146 population.

148 *2.3.2. Participant screening*

149 All children with symptoms of nausea and fulfilling the Rome IV criteria for CIN or FD, will
150 undergo blood laboratory testing before inclusion, including complete blood cell count, C-
151 reactive protein, liver function tests, creatinine, total bilirubin, and for celiac screening,
152 amylase anti-transglutaminase antibodies and IgA testing. Additionally, urinalysis and stool
153 analysis for parasites (*Giardia Lamblia*, *Entamoeba Histolytica*) and *Helicobacter pylori*
154 antigens will be performed. The need for additional diagnostic testing, for example

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155 endoscopy to rule out eosinophilic esophagitis or 24h pH, will be left to the discretion of the
156 treating pediatrician or pediatric gastroenterologist. The flow of the study protocol is
157 presented in Figure 2.

158

159 **2.4. Criteria**

160 *2.4.1. Inclusion criteria*

161 A total sample of 100 children and adolescents with CIN or FD with symptoms of nausea will
162 be enrolled in the study. Children and adolescents can participate in this study if they meet
163 the following inclusion criteria:

- 164 • Age 8 to 18 years at inclusion of the study
- 165 • Diagnosis of CIN or FD, with symptoms of nausea, according to Rome IV criteria
166 (Hyams et al., 2016)
- 167 • Sufficient knowledge of the Dutch language

168 *2.4.2. Exclusion criteria*

169 Children will not be enrolled in the study if they meet the following exclusion criteria:

- 170 • Concomitant organic gastrointestinal disease
- 171 • Simultaneous treatment by another health care professional for symptoms of nausea
- 172 • Previously received hypnotherapy
- 173 • Intellectual disability

174 **2.5. Randomization, blinding, and treatment allocation**

175 After obtaining informed consent, children are randomly allocated, by the treating
176 pediatricians, to one of the two treatment arms: HT, given by a qualified therapist, or SMT,
177 meaning treatment by the child's pediatrician. A computerized random-number generator
178 will be used to randomly allocate children on a 1:1 basis with varying block sized of 2, 4 and
179 6. To ensure allocation concealment, central randomization will be applied and the random
180 allocation sequence remains concealed from pediatricians enrolling children into the study.
181 Due to the nature of HT, it is not possible to blind the participating children and health care
182 professionals involved in the treatment of the participants.

183 **2.6. Intervention**

184 *2.6.1. Hypnotherapy*

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1
2
3 185 Individual HT consist of 6 sessions of 50-60 minutes, given over a period of 3 months by a
4
5 186 qualified hypnotherapist (week 1, 2, 3, 5, 7 and 11). Twelve hypnotherapist affiliated to the
6
7 187 recruiting hospitals will offer the HT to children. All hypnotherapists have years of
8
9 188 experience in performing HT in children. The hypnotherapists will use an adapted version of
10
11 189 our previously used HT protocol [13, 20]. The HT protocol contains exercises focusing on
12
13 190 normalization of the gut motility, stress reduction and ego strengthening. The
14
15 191 hypnotherapists will be instructed to use the same scripts, but are allowed to adapt the
16
17 192 content to the child's needs. The same protocol is used for children of all ages. However, the
18
19 193 language used will be adjusted to the child's developmental age.

19 194 In the first session, an introduction to HT will be given to the child and parents, including an
20
21 195 explanation of what HT is and how it may help in reducing symptoms of nausea.

22
23 196 Furthermore, the hypnotherapist will take a full history and children and parents are
24
25 197 instructed to not talk about the nausea during the treatment period. The hypnotherapist will
26
27 198 then start with a breathing exercise and introduce a progressive relaxation, in which children
28
29 199 imagine floating on a big cloud. Positive suggestions to increase the child's belly comfort will
30
31 200 also be provided. For instance, the child will be instructed to make hands warm and place
32
33 201 both hands on the belly, imagining warmth spreading through their abdomen, and especially
34
35 202 the stomach.

36 203 In the second session, the therapist will repeat the exercise on progressive relaxation.

37
38 204 Additionally, the therapist will introduce an exercise focusing on reduction of anxiety and
39
40 205 stress, which is called 'the favorite place exercise'.

41
42 206 The third session focuses on ego strengthening and a new exercise will be introduced: 'the
43
44 207 rainbow planet exercise' for children attending primary school, and 'the air balloon exercise'
45
46 208 for children in secondary school. In the first exercise, children choose a personal need from a
47
48 209 rainbow that contains different needs, for example a healthy stomach, courage, tranquility,
49
50 210 or confidence.

51 211 In the fourth session, children are encouraged to release stress during the 'the beach
52
53 212 without worries exercise' and additional ego strengthening suggestions are made.

54 213 The fifth session focuses on reduction of anxiety, stress and ego strengthening, as well as
55
56 214 improved functioning of the digestive system. For the digestive system, children visualize a
57
58 215 well working digestive system with food sliding through the stomach and bowel in a
59
60 216 comfortable way.

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1
2
3 217 In the sixth session, the previous sessions will be evaluated, remaining gastro-intestinal
4
5 218 problems may be addressed and preceding exercises may be repeated, if requested by
6
7 219 children. If no improvement has taken place, an exercise will be introduced in which the
8
9 220 child is instructed to look inside the stomach to see 'what the stomach needs'.

10 221 After the first session, all children will receive a CD containing standard scripts of the
11
12 222 exercises used during the sessions. The hypnotherapist will advise children to self-practice
13
14 223 these exercises on a daily basis. Additionally, the therapist will encourage children to
15
16 224 practice breathing exercises a few time a day.

17
18 225

19 226 *2.6.2. Standard medical care + supportive therapy*

20 227 In the SMT group, children will visit their treating pediatrician 6 times over a 3-month
21
22 228 period. All pediatricians will be instructed to use the same protocol for treating symptoms of
23
24 229 nausea. The protocol consists of a stepwise approach. In the first step, children and parents
25
26 230 will be educated about CIN and FD, reassured that there is no structural organic underlying
27
28 231 disease present, and dietary and lifestyle advices will be provided. Children will be advised to
29
30 232 adhere to national practical guidelines for healthy eating by the Netherlands Nutrition
31
32 233 Centre. Children will be recommended to avoid products containing caffeine, strong spices,
33
34 234 citrus fruits, onions, fatty foods, and if applicable, to stop smoking. Additionally, the
35
36 235 pediatrician will explore, together with children and parents, possible connections between
37
38 236 stressful moments, emotional problems and complaints of nausea. If connections are
39
40 237 present, the pediatrician will encourage children and parents to improve coping strategies to
41
42 238 effectively manage stress, to reduce external stressors, and to ensure an optimal
43
44 239 environment with sufficient relaxation. Children will also be encouraged to continue their
45
46 240 normal daily and sport activities and to go to school, to prevent or decrease avoidance
47
48 241 behavior.

49 242 In case this does not result in adequate relief of symptoms, the pediatrician continues with
50
51 243 the second step. In the second step, proton pump inhibitors (PPI) in combination with
52
53 244 domperidone will be prescribed. If this treatment is not effective in reducing symptoms the
54
55 245 pediatrician continues with the third step, which includes the prescription of ondansetron
56
57 246 and (dis)continuation of PPIs. If again no adequate improvement occurs, in the fourth step,
58
59 247 Iberogast will be started for children >12 years. If children do not respond to Iberogast (>12
60
248 years) or ondansetron (<12 years), the pediatrician will continue with the fifth step and

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1
2
3 249 prescribe erythromycin. Finally, if previous treatment did not prove to be successful in
4
5 250 reducing symptoms, cyproheptadine will be prescribed.
6
7 251 The pediatrician will evaluate each step after two to four weeks. All dosages, except for
8
9 252 Iberogast, will be prescribed according to www.kinderformularium.nl (Dutch medical
10
11 253 guideline for pediatricians).
12
13 254 In addition to the medical treatment, children will receive 6 half hour sessions of supportive
14
15 255 therapy given by the treating pediatrician. In these sessions, the symptom progression will
16
17 256 be discussed and patient education will be provided. Moreover, exploration of potential
18
19 257 contributing triggers (i.e. dietary product, emotional problems and stressful events) will be
20
21 258 evaluated together with children and parents. Supportive therapy is added to correct for the
22
23 259 patient-therapist time in the HT group.

24
25 260

26 261 *2.6.3. Co-interventions*

27 262 After 6 sessions of HT, children visit their pediatrician to evaluate the effects of HT and, if
28
29 263 considered necessary, to receive additional medical care.

30
31 264

32 265 **2.7. Outcomes**

33 266 *2.7.1. Primary outcome*

34 267 The primary outcome of the RCT is the proportion of patients with at least 50% reduction of
35
36 268 their symptoms of nausea compare to baseline at 12 months follow-up. Children and
37
38 269 adolescents report symptoms of nausea at home by using the 7-day diary. To promote
39
40 270 retention and complete follow-up, children and parents will be reminded on regular basis,
41
42 271 via email and phone calls, to fill in the 7-day diary and other questionnaires.
43
44 272

45
46 273

47 274 *7-day diary*

48
49 275 The 7-day diary is used by children and adolescents to score the severity, incidence and
50
51 276 frequency of symptoms of nausea, every day during 7 consecutive days [13, 21, 22].

52
53 277 The *severity* of nausea is assessed by the 'nausea face' analog scale, a validated tool in the
54
55 278 pediatric population [23]. Children rate their degree of nausea on a day using 6-faces: face 0
56
57 279 indicates no nausea and face 6 indicates nausea as bad as it can be imaged. Scores on the
58
59 280 'nausea face' scale are transported to a daily 0-10 score. Face 0, no nausea, is scored as 0,
60
face 1 is scored as 2, face 2 is scored as 4, face 3 is scored as 6, face 4 is scored as 8 and face

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1
2
3 281 5 is scored as 10 [23]. The 'severity of nausea' (SON) score is calculated by summing up the
4
5 282 scores of seven days, giving a maximum of score of 70 [13, 20- 22].

6
7 283 The *incidence* of nausea is assessed using the 'nausea incidence' scale (NIS), adapted from
8
9 284 the 5-point dyspepsia Likert scale (Canan, 2011; De Luca et al., 2004). It measures the
10
11 285 incidence of symptoms during a day, where score 0 for no nausea, score 1 for 1-2 times a
12
13 286 day, score 2 for 3-5 times a day, score 3 for intermittent complaints and score 4 for
14
15 287 complaints were always present. The total sum of the scores of seven days indicates the
16
17 288 severity of the nausea during a week, as experienced by the child. The maximum total score
18
19 289 is 28 [13, 20- 22].

20 290 The *frequency* of symptoms of nausea is recorded in minutes/hours per day and is scored by
21
22 291 children as 0 when there was no nausea, 1 if children had <10 minutes of nausea, 2 for 10-30
23
24 292 minutes of nausea, 3 for 30 minutes-2 hours of nausea, 4 for 2-4 hours of nausea and 5 if the
25
26 293 nausea lasts >4 hours a day. The 'nausea frequency score' (NFS) is calculated by summing
27
28 294 the scores of the seven days, with a maximum of 35 [13, 21, 22]. Treatment success is
29
30 295 defined as at least 50% reduction in the SON, NIS and NFS.

31 296

32 297 *2.7.2. Secondary outcomes*

33
34 298 In addition to the primary outcomes, the present study investigates secondary outcomes,
35
36 299 including abdominal pain, dyspeptic symptoms, health related quality of life, anxiety,
37
38 300 depression, school absences, parental absence of work and health-care costs. Secondary
39
40 301 outcomes are measured at 6 weeks and 3 months after treatment, and at 6 and 12 months
41
42 302 follow-up after the end of treatment (Figure 1).

43 303

44 304 *Abdominal pain*

45
46 305 A 7-day diary is used to assess the severity and frequency of abdominal pain, every day
47
48 306 during 7 consecutive days. It comprises of two subscales: the abdominal pain intensity
49
50 307 subscale (APIS) and abdominal pain frequency subscale (APFS). The APIS will be scored using
51
52 308 an affective facial scale ranging with face 0 indicating 'no pain at all' to face 5 indicating 'the
53
54 309 most severe pain'. No abdominal pain is scored as 0, faces 1 - 2 are scored as 1, faces 3 - 4
55
56 310 are scored as 2 and face 5 is scored as 3. The scores of seven days are summed up, with a
57
58 311 maximum score of 21 [13, 20- 22]. The APFS is recorded in minutes/hours of abdominal pain
59
60 312 per day, with score 0 indicating no pain, score 1 if children had <10 minutes of pain, 2 for 10-

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313 30 minutes of pain, 3 for 30 minutes-2 hours of pain, 4 for 2-4 hours of pain and 5 >4 hours
314 of pain. The scores the APFS are summed up, giving a pain frequency score of maximum 35
315 [13, 20- 22].

316 *Dyspeptic symptoms*

317 Severity and incidence of dyspeptic symptoms is measured using the 5-point dyspepsia
318 Likert scale, previously used in the pediatric population [24, 25]. The dyspepsia Likert scale
319 consists of 8 gastrointestinal dyspeptic symptoms: epigastric pain, upper abdominal
320 discomfort, retrosternal pyrosis, sour-bitter taste, halitosis, belching, nausea, and early
321 satiety. Children score the *severity* of each symptoms during the previous two weeks on a 5-
322 point Likert scale: score 1 'no complaints at all', score 2 'little complaints', score 3 'moderate
323 complaints', score 4 'quite a lot of complaints' and 5 'serious complaints' [24]. A higher sum
324 score indicates more severe dyspeptic complaints (SDC score), with a maximum of 40.
325 Children report on the *incidence* of each of the symptoms during the previous two weeks by
326 scoring: 1 'no complaints', 2 '1-2 times a week', 3 '3-5 times a week', 4 'intermittent
327 complaints' and 5 'complaints were always present' [24]. The dyspepsia severity score (DSS)
328 is calculated by summing up the scores, giving a maximum value of 40.

329 *Health related quality of life*

330 The KIDSCREEN-52 questionnaire measures health related quality of life (QoL) in children
331 and adolescents. The questionnaire has been shown a valid tool in the Dutch pediatric
332 population [26, 27]. The KIDSCREEN-52 consists of items on ten dimensions related to QoL
333 on a 5-point Likert scale: moods and emotions, self-perception, relations with parents and
334 home life, autonomy, physical well-being, psychological well-being, school environment,
335 social support and peers, social acceptance (bullying) and financial resources. For each
336 individual dimension, Rasch scores are computed from the individual items. These are then
337 transformed into T-values: higher T-values indicate a better health related QoL and well-
338 being.

339 *Anxiety and depression*

340 Anxiety and depression are evaluated using the Revised Anxiety and Depression Scale-short
341 version (RCADS-25). This questionnaire has been previously validated in the Dutch pediatric
342 population [28]. The RCADS-25 consists of five subscales measuring symptoms of generalized
343 anxiety disorders, separation anxiety disorder, social phobia, panic disorder and major
344 depressive disorder. Each subscale contains five items and scales range from 0 (never) to 3

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1
2
3 345 (always). The total score on anxiety or depression is the sum of the items measuring
4
5 346 symptoms of anxiety and depressive symptoms, respectively. Higher scores indicate more
6
7 347 symptoms of anxiety or depression.

8
9 348 *Cost effectiveness/cost utility*

10 349 The Health Utility Index Mark 3 (HUI) will be used in the cost-utility and cost-effectiveness
11
12 350 analysis. The HUI-3 is a multi-attribute utility measure of health status in children as
13
14 351 reported by parents. Proxy measurements of parents for health status of children are
15
16 352 justifiable, as some children may be too young to provide reliable and valid information
17
18 353 about their own health status [29-31]. The questionnaire consists of eight dimensions of
19
20 354 health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain,
21
22 355 with scales varying from highly impaired to normal. Health utilities of 1 indicate perfect
23
24 356 health, whereas 0 indicates death. The Quality adjusted life years (QALY) will be calculated
25
26 357 by multiplying the sum of the utility of health states by the time in between measurements.

27 358 *Work absenteeism by parents and school absenteeism by children*

28
29 359 An adapted version of the Dutch Health and Labor Questionnaire (HLQ) will be used to
30
31 360 measure work absenteeism by parents, school absenteeism by children, and indirect costs of
32
33 361 health care utilization [32]. This adapted version contains three items. Parents indicate
34
35 362 whether their child has been absent from school due to complaints of nausea, and if yes, the
36
37 363 amount of hours per week. For work absenteeism by parents, parents indicate the number
38
39 364 of hours they worked less on average because of their child's symptoms of nausea. For the
40
41 365 indirect costs of health care utilization, parents indicate additional costs they had due to
42
43 366 symptoms of nausea of their child over the past four weeks.

44 367 *Somatization*

45 368 The Children's Somatization Inventory (CSI) measures the extent to which children and
46
47 369 adolescents experience somatic symptoms. The questionnaire has been shown a valid and
48
49 370 reliable self-report instrument in the pediatric population [33]. The CSI consists of 35 items
50
51 371 and on a 5-point Likert scale (0 = not at all to 4 = a whole lot) and children rate the extent to
52
53 372 which they experienced somatic symptoms in the previous two weeks. The total score is
54
55 373 calculated by summing up the 35 items, with higher scores indicating higher intensity of
56
57 374 somatic complaints experienced by the child.

58 375 In order to calculate a separate CSI-score for non-gastrointestinal (GI) symptoms, 7 items on
59
60 376 GI-symptoms (nausea, constipation, diarrhea, epigastric and abdominal pain, vomiting and

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1
2
3 377 bloating) are left out. The total score of somatic symptoms without GI-symptoms is
4
5 378 calculated by summing up the scores of non-GI symptoms, with higher scores reflecting
6
7 379 higher intensity of non-GI somatic complaints.

8 380 *Adequate relief*

9
10 381 Parents and children will be asked whether adequate relief of symptoms of nausea has
11
12 382 occurred, using a dichotomous scale (yes/no). Adequate relief has been previously used as
13
14 383 an endpoint in clinical trials assessing hypnotherapy in children and adolescents [20] and has
15
16 384 been shown a valid outcome measure for functional gastrointestinal disorders [34].
17

18 385

19 386 **2.8. Sample size calculation**

20
21 387 The primary outcome of the RCT is the proportion of patients with at least 50% reduction of
22
23 388 their symptoms of nausea compare to baseline at 12 months follow-up. Based on our pilot
24
25 389 study (Vlieger, A. M. "A pilot-study of hypnotherapy as a treatment for functional nausea in
26
27 390 children") and the success percentages in studies using hypnotherapy in adults with
28
29 391 functional dyspepsia [35] and in pediatric cancer patients [14] , we expect that 80% of the
30
31 392 children in the hypnotherapy group will have >50% reduction of their symptoms of nausea
32
33 393 after one year. In the standard medical care group, we anticipate that 50% of the children
34
35 394 will have >50% reduction of their symptoms of nausea after one year. Based on these
36
37 395 expected proportions, 45 children per group will be needed to achieve a power of 80% with
38
39 396 a one-sided significance level of 5%. Accounting for a 10% dropout, 100 children will be
40
41 397 included in this study. If a child is prematurely withdrawn from the study, he/she will not be
42
43 398 replaced; data will be analyzed according to the intention to treat analysis.

44 399 **2.9. Statistical analysis**

45 400 *2.9.1. Primary outcome*

46
47 401 Outcomes will be analyzed according to the intention to treat (ITT) analysis. For the primary
48
49 402 outcome, the Chi-square test will be used to compare the proportions of patients with >50%
50
51 403 reduction of symptoms of nausea (i.e. severity, incidence and frequency of nausea) after 12
52
53 404 months follow-up between the two groups (HT versus SMT). For all analysis, the significance
54
55 405 level for statistical analysis is set at $\alpha = 0.05$. Multiple imputation will be applied to deal with
56
57 406 cases of missing data.
58

59 407
60

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408 2.9.2. Secondary outcomes

409 For the secondary outcomes, including the potential influence on abdominal pain, dyspeptic
410 symptoms, health related quality of life, anxiety, depression, work absenteeism by parents,
411 school absenteeism by children, somatization and adequate relief, the Student's *t*-test will
412 be used for means of normally distributed data, the Mann–Whitney U test for
413 nonparametric data and the Chi-square test to compare proportions. To calculate the cost-
414 effectiveness, cost-utility and cost-effectiveness ratios will be calculated for the extra costs
415 per child with >50% reduction of symptoms of nausea and the extra costs per QALY.
416 As secondary analysis, the proportion of patients with >50% reduction of their nausea
417 (severity, incidence and frequency) after treatment, 6 months and 12 months follow up will
418 be compared between groups using multivariate logistic regression correcting for age and
419 center.

420

421 3. Amendments

422 Prior to implementation, amendments will be examined and approved by the METC. The
423 sponsor will only record non-substantial amendments.

424 4. Data monitoring

425 Hypnotherapy is usually well tolerated in children, without significant side effects. In our
426 previous trials only a minority of children reported some dizziness, mostly during or directly
427 after the end of the first session [13, 21]. In case children experience dizziness, they will be
428 advised to execute the remaining sessions in a sitting position instead of a supine position.
429 Children assigned to the SMT group will receive standard medical treatment, including drugs
430 that have been either registered for children, or of which side effects are limited and well
431 known. For these reasons, no Data Monitoring Safety Board will be established.
432 Study auditing will be accomplished by periodic visits to the participating centers, and by
433 email and telephone contact with local investigators, to ensure the study protocol is being
434 complied with and to discuss any problems that might have arisen.

435 5. Potential harms

436 In accordance to the legal requirements in the Netherlands (article 10, subsection 1, WMO),
437 the investigator will inform the subjects and the reviewing accredited METC if harmful
438 events occur. When there are indications that the disadvantage of participation may be

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1
2
3 439 significantly greater than was described in the research proposal, the study will be
4
5 440 suspended pending further review by the accredited METC. However, the study will not be
6
7 441 suspended if it would jeopardize participating children's health.

9 442 **6. Ancillary and post-trial care**

11 443 In accordance with Article 7 WMO and the Measure regarding Compulsory Insurance for
12
13 444 Clinical Research in Humans of 23th June 200th, the sponsor has liability insurance for any
14
15 445 damage to children which might emerge from study participation [36].

17 446 **7. Data storage**

19 447 The related information on paper, including 7-day diaries, will be securely stored in a locked
20
21 448 file cabinet with limited access. Online questionnaire data will be securely stored using the
22
23 449 University's password-protected access systems. Only the main researchers will be given full
24
25 450 access to the questionnaire data. All records that contain names will be saved in one file,
26
27 451 which will be password protected and only accessible to the main researchers.

30 453 **8. Dissemination policy**

32 454 The researchers will communicate trial results to the public, health care providers, and other
33
34 455 relevant groups via reports, and by publishing in peer-reviewed journals. Negative as well as
35
36 456 positive results will be published. The results will be shared with participating children and
37
38 457 parents after completion of the trial. All authors who provided substantial contributions to
39
40 458 the conduct, interpretation, and reporting of the results will be granted authorship on the
41
42 459 final trial report.

45 461 **9. Discussion and conclusion**

47 462 Chronic nausea is a highly disabling symptom for children with CIN or FD, and poses a risk for
48
49 463 negative health outcomes and decreased psychosocial functioning [2-4]. To date large
50
51 464 randomized placebo controlled trials evaluating the effect of any drug in children with either
52
53 465 CIN or FD are lacking [37]. Current medical treatment is experienced based, however these
54
55 466 treatments are symptomatic and often used for months or years [7, 8]. For these reasons,
56
57 467 new effective treatment options to reduce nausea in children with CIN or FD are warranted.

58 468
59 469 There are indications that HT can decrease symptoms of functional nausea and dyspepsia in

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1
2
3 470 adults [35], and functional abdominal pain (FAP) [13] and chemotherapy induced nausea in
4
5 471 children [14]. Calvert et al. (2002) found that adult patients with FD receiving 12 sessions of
6
7 472 HT had significantly less dyspeptic symptoms (59%, N=26) compared to patients receiving
8
9 473 medical treatment (33%, N=29) ($p=0.02$) [35]. These beneficial effects were maintained for
10
11 474 more than a year: 56 weeks after the first treatment, 73% of the patients in the HT group
12
13 475 reported symptom improvement compared to 43% in the medical treatment group ($p<0.01$).
14
15 476 In children with FAP, Vlieger (2007) found that HT was highly superior compared to standard
16
17 477 medical care to reduce abdominal pain. At one year follow-up, 85% of the children in the HT
18
19 478 group (N=26) were in clinical remission compared to 25% of the children in the SMT group
20
21 479 (N=24) ($p<0.001$) [13]. Additionally, a systematic review including six RCTs evaluating the
22
23 480 effectiveness of hypnotherapy to reduce chemotherapy-induced nausea found
24
25 481 hypnotherapy was most effective when compared with standard medical care to reduce
26
27 482 complaints ($D=0.99$) [14].

27 483

28
29 484 The present study is the first study to investigate the effectiveness of HT on symptoms of
30
31 485 nausea in children and adolescents diagnosed with CIN or FD, according to the Rome IV
32
33 486 criteria. If shown effective, it may provide an additional treatment option for children with
34
35 487 CIN or FD.

36 488 The study has several strengths. The first strength is that pediatricians from eleven different
37
38 489 hospitals throughout the Netherlands will recruit all children and adolescents. The hospitals,
39
40 490 both an academic center and teaching hospitals, serve an ethnic and socio-economic diverse
41
42 491 population of children and adolescents. This recruitment method has two advantages: first,
43
44 492 it may reduce response bias to the intervention. It has previously been reported that
45
46 493 patients from primary and secondary level care may have different responses to treatment
47
48 494 [38]. All children included in the present study receive secondary level care. The second
49
50 495 advantage is that the multicenter design of the study will increase generalizability of the trial
51
52 496 outcomes.

53 497 Another strength of the study is the long-term follow up of one year, which allows us to
54
55 498 properly compare the potential effectiveness of HT with SMT. It has been known that the
56
57 499 severity of functional gastrointestinal symptoms in children varies over time [39] and a
58
59 500 continuous improvement in symptoms is often reported in children receiving hypnotherapy
60
61 501 [13].

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1
2
3 502 This study also has several limitations. The first limitation is that children, parents,
4
5 503 investigators and health care providers are not blinded for the received treatments, which is
6
7 504 not possible due the nature of HT. Several solutions will be applied to limit the risk of bias.
8
9 505 First, to minimize performance bias, pediatricians and hypnotherapists will follow treatment
10
11 506 guidelines to prevent any use of additional or alternative forms of care during the study
12
13 507 period that may influence treatment outcomes. Second, to reduce the risk of detection bias,
14
15 508 children and adolescents use reliable outcome measures and record symptoms themselves
16
17 509 at home. Moreover, children and adolescents record symptoms of nausea for seven
18
19 510 consecutive days, which corrects for individual variability of symptoms over time. Third, the
20
21 511 endpoints of the study will be preregistered.
22
23 512 The second limitation is that the SMT provided by pediatricians in this study may not reflect
24
25 513 usual clinical practice. In the present study, children and adolescents receive longer and
26
27 514 more intensive medical therapy from their pediatrician compared to the real medical
28
29 515 practice situation. However, previous studies indicate that patient-provider interactions can
30
31 516 largely influence gastrointestinal treatment outcomes [40]. Therefore, it is important to
32
33 517 control for the time spent per patient in the SMT group.
34
35 518 If the results of this study show that HT given by a therapist is comparable or slightly more
36
37 519 effective than medical treatment provided by pediatricians, HT may become a new
38
39 520 treatment strategy to help children with CIN or FD. Furthermore, as HT is presumably less
40
41 521 costly than treatments by a specialist it may also decrease health care costs.

42 522 **Abbreviations**

43 523 **APIS:** Abdominal Pain Intensity Subscale; **APFS:** abdominal pain frequency subscale; **CIN:**
44 524 Chronic Idiopathic Nausea; **CSI:** Children's Somatization Inventory; **FAP:** Functional
45 525 Abdominal Pain; **FD:** Functional Dyspepsia; **FGID:** Functional Gastrointestinal Disorders; **GI:**
46 526 gastrointestinal; **HLQ:** Health and Labor Questionnaire; **HT:** Hypnotherapy; **HUI:** Health
47 527 Utility Index Mark 3; **ITT:** Intention to Treat Analysis; **MEC-U:** Medical Research Ethics
48 528 Committees United; **NIS:** Nausea Incidence Scale; **NFS:** Nausea Frequency Score; **PPI:** Proton
49 529 Pump Inhibitors; **QALY:** Quality Adjusted Life Years; **QoL:** Health related Quality of Life;
50 530 **RCADS-25:** Revised Anxiety and Depression Scale-short version; **RCT:** Randomized Controlled
51 531 Trial; **REC:** Research Ethical Committees; **SMT:** Standard Medical Care plus supportive
52 532 therapy; **SON:** Severity Of Nausea; **WMO:** Medical Research Involving Human Subjects Act

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1
2
3 533 **Acknowledgements**

4
5 534 None

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7
8 535 **Competing interests**

9 536 The authors declare no competing interests.

10
11
12 537 **Funding**

13
14 538 The Christine Bader Foundation and Gastrointestinal and Liver Foundation supported this
15 539 work. These funding sources had no role in the design of this study. They will not have any
16 540 role during the collection of data, analyses or submission of the results.

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20 541 **Author contributions**

21 542 AV is the principle investigator, designed the study, wrote the protocol, supervised the trial
22 543 and supervised writing the manuscript. PB provided adjustments to the protocol, drafted the
23 544 manuscript and coordinated the trial. MB critically revised the protocol, supervised the trial
24 545 and supervised writing the manuscript. BdH, ES, HvW, WTAT, EK, MG, NB, MW, MvdB, JG,
25 546 ST, CF participated in patient recruitment and/or treatment, read and approved the
26 547 manuscript.

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30 548 **Trial status**

31 549 Recruitment started in September 2016 and is ongoing. In October 2016, the first participant
32 550 enrolled. Currently, 92 children are participating in the study (18 of them have completed
33 551 the study protocol).

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36 552 **Ethics approval and consent to participate**

37 553 This RCT was approved by the Medical Research Ethics Committees United (MEC-U) in
38 554 Nieuwegein, the Netherlands (file number: NL51167.100.15). The study will be conducted in
39 555 accordance with the Medical Research Involving Human Subjects Act (WMO) and conferring
40 556 to the principles of the Declaration of Helsinki [36]. (64th WMA General Assembly, Fortaleza,
41 557 Brazil, October 2013). The study will follow the conduct code concerning resistance in
42 558 minors who participate in clinical trials as defined by the Dutch Pediatric Society. Informed
43 559 consent will be asked from parents/guardians of children <12 years of age. In children and
44 560 adolescents ≥ 12 years of age informed consent will be asked from the parents-guardians
45 561 and the children and adolescents. In the event of amendments of the protocol, relevant

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562 research ethical committees (RECs) will be informed. Results of the study will be publically
563 disclosed in a peer-reviewed journal, without any restrictions; both positive as well as
564 negative results will be published.

565 **5 peer reviewers suggested**

566 Miguel Saps (msaps@childrensmemorial.org), Miranda van Tilburg (Tilburg@med.unc.edu),
567 Peter Whorwell (peter.whorwell@smuht.nwest.nhs.uk), Olafur Palsson
568 (opalsson@med.unc.edu), Juliette Rutten (j.m.rutten@amc.uva.nl), Emma Louise Calvert.

569 **Figure legends**

570 **X**

571 **Figure 1.** Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure
572 displaying the trial design and the outcome measurements. After screening for eligibility (t-
573 1), children and parents sign the informed consent form and fill in the baseline questionnaire
574 (t0). Children are then randomized in the hypnotherapy (HT) or standard medical care (SMT)
575 group. Assessments take place before the start of treatment (baseline; t0), 6 weeks after the
576 start of treatment (t1), 3 months after the start of treatment (t2), 6 months follow-up (t3)
577 and 12 months follow-up (t4).

578
579 **X**

580 **Figure 2.** The Consolidated Standards of Reporting Trials (CONSORT) flow diagram indicating
581 the number of participants throughout the study. After eligibility screening, children are
582 randomized in either the hypnotherapy (HT) or standard medical care (SMT) group. Follow-
583 up measurements take place at 6 weeks after the start of treatment (t1), 3 months after the
584 start of treatment (t2), and 6 months follow-up (t3) and 12 months follow-up (t4).

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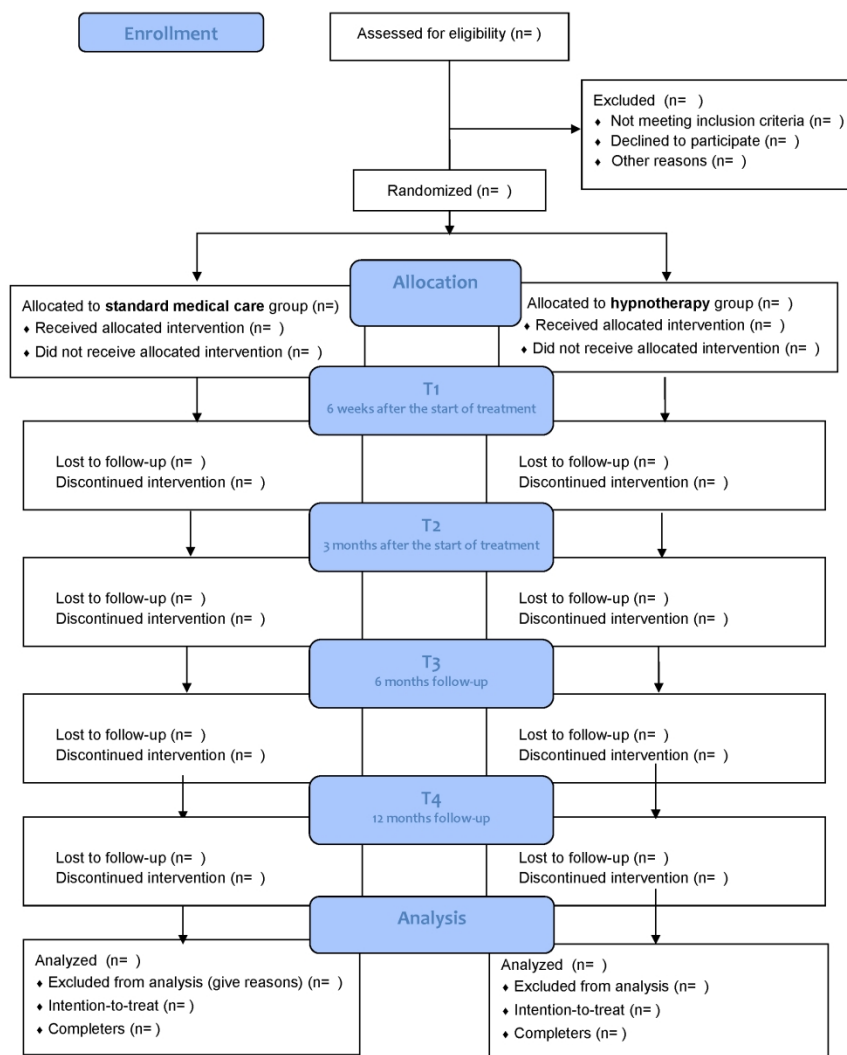
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TIMEPOINT	Enrolment	Allocation	During treatment		Follow-up	
	Before treatment (t-1)	Start of treatment (t0)	6 weeks after the start of treatment (t1)	3 months after the start of treatment (t2)	6 months follow-up (t3)	12 months follow-up (t4)
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization	X					
INTERVENTIONS:						
Hypnotherapy group (HT)		←————→				
Standard medical care group (SMT)		←————→				
ASSESSMENTS:						
Nausea and abdominal pain	X		X	X	X	X
Dyspeptic symptoms		X		X	X	X
Health related quality of life		X		X	X	X
Anxiety and Depression		X		X	X	X
Cost effectiveness/cost utility		X		X	X	X
Work absenteeism by parents and school absenteeism by children		X		X	X	X
Somatization		X		X	X	X
Adequate relief					X	X

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure displaying the trial design and the outcome measurements. After screening for eligibility (t-1), children and parents sign the informed consent form and fill in the baseline questionnaire (t0). Children are then randomized in the hypnotherapy (HT) or standard medical care (SMT) group. Assessments take place before the start of treatment (baseline; t0), 6 weeks after the start of treatment (t1), 3 months after the start of treatment (t2), 6 months follow-up (t3) and 12 months follow-up (t4).

215x279mm (300 x 300 DPI)



45 Figure 2. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram indicating the number of
46 participants throughout the study. After eligibility screening, children are randomized in either the
47 hypnotherapy (HT) or standard medical care (SMT) group. Follow-up measurements take place at 6 weeks
48 after the start of treatment (t₁), 3 months after the start of treatment (t₂), and 6 months follow-up (t₃) and
49 12 months follow-up (t₄).

50 215x279mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3-14
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 18
Roles and	#5b	Name and contact information for the trial sponsor	18

1	responsibilities:			
2	sponsor contact			
3	information			
4				
5				
6	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	18
7	responsibilities:		collection, management, analysis, and interpretation of	
8	sponsor and funder		data; writing of the report; and the decision to submit the	
9			report for publication, including whether they will have	
10			ultimate authority over any of these activities	
11				
12				
13				
14	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	NA
15	responsibilities:		centre, steering committee, endpoint adjudication	
16	committees		committee, data management team, and other individuals or	
17			groups overseeing the trial, if applicable (see Item 21a for	
18			data monitoring committee)	
19				
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22				
23	Background and	#6a	Description of research question and justification for	3, 4
24	rationale		undertaking the trial, including summary of relevant studies	
25			(published and unpublished) examining benefits and harms	
26			for each intervention	
27				
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30	Background and	#6b	Explanation for choice of comparators	5
31	rationale: choice of			
32	comparators			
33				
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35	Objectives	#7	Specific objectives or hypotheses	4
36				
37				
38	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
39			group, crossover, factorial, single group), allocation ratio,	
40			and framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
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44				
45	Study setting	#9	Description of study settings (eg, community clinic,	5
46			academic hospital) and list of countries where data will be	
47			collected. Reference to where list of study sites can be	
48			obtained	
49				
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52	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6
53			eligibility criteria for study centres and individuals who will	
54			perform the interventions (eg, surgeons, psychotherapists)	
55				
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58	Interventions:	#11a	Interventions for each group with sufficient detail to allow	7-9
59				
60				

1	description		replication, including how and when they will be administered	
2				
3				
4	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9, 15
5	modifications			
6				
7				
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11	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
12	adherence			
13				
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17	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
18	concomitant care			
19				
20				
21	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	9-13
22				
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32	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)	5
33				
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40	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
41				
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47	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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51	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign	6-7
52	generation			
53				
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1			interventions	
2				
3	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6-7
4	concealment		central telephone; sequentially numbered, opaque, sealed	
5	mechanism		envelopes), describing any steps to conceal the sequence	
6			until interventions are assigned	
7				
8				
9				
10	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	6-7
11	implementation		participants, and who will assign participants to	
12			interventions	
13				
14				
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	6-7
16			trial participants, care providers, outcome assessors, data	
17			analysts), and how	
18				
19				
20				
21	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	NA
22	emergency		permissible, and procedure for revealing a participant's	
23	unblinding		allocated intervention during the trial	
24				
25				
26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	9-13
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
33				
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38	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	9
39	retention		up, including list of any outcome data to be collected for	
40			participants who discontinue or deviate from intervention	
41			protocols	
42				
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45	Data management	#19	Plans for data entry, coding, security, and storage, including	15
46			any related processes to promote data quality (eg, double	
47			data entry; range checks for data values). Reference to	
48			where details of data management procedures can be	
49			found, if not in the protocol	
50				
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54	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	14-15
55			outcomes. Reference to where other details of the statistical	
56			analysis plan can be found, if not in the protocol	
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1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	NA
2	analyses		adjusted analyses)	
3				
4				
5	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	14
6	population and		adherence (eg, as randomised analysis), and any statistical	
7	missing data		methods to handle missing data (eg, multiple imputation)	
8				
9				
10	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	15
11	formal committee		of its role and reporting structure; statement of whether it is	
12			independent from the sponsor and competing interests; and	
13			reference to where further details about its charter can be	
14			found, if not in the protocol. Alternatively, an explanation of	
15			why a DMC is not needed	
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20	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	NA
21	interim analysis		including who will have access to these interim results and	
22			make the final decision to terminate the trial	
23				
24				
25				
26	Harms	#22	Plans for collecting, assessing, reporting, and managing	15
27			solicited and spontaneously reported adverse events and	
28			other unintended effects of trial interventions or trial conduct	
29				
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31				
32	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	15
33			and whether the process will be independent from	
34			investigators and the sponsor	
35				
36				
37	Research ethics	#24	Plans for seeking research ethics committee / institutional	P1
38	approval		review board (REC / IRB) approval	
39				
40				
41	Protocol	#25	Plans for communicating important protocol modifications	14
42	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
43			relevant parties (eg, investigators, REC / IRBs, trial	
44			participants, trial registries, journals, regulators)	
45				
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47				
48	Consent or assent	#26a	Who will obtain informed consent or assent from potential	19
49			trial participants or authorised surrogates, and how (see	
50			Item 32)	
51				
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54	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
55	ancillary studies		participant data and biological specimens in ancillary	
56			studies, if applicable	
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1	Confidentiality	#27	How personal information about potential and enrolled	15
2			participants will be collected, shared, and maintained in	
3			order to protect confidentiality before, during, and after the	
4			trial	
5				
6				
7				
8	Declaration of	#28	Financial and other competing interests for principal	18
9	interests		investigators for the overall trial and each study site	
10				
11				
12	Data access	#29	Statement of who will have access to the final trial dataset,	15
13			and disclosure of contractual agreements that limit such	
14			access for investigators	
15				
16				
17	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	15
18	trial care		compensation to those who suffer harm from trial	
19			participation	
20				
21				
22				
23	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	16
24	trial results		results to participants, healthcare professionals, the public,	
25			and other relevant groups (eg, via publication, reporting in	
26			results databases, or other data sharing arrangements),	
27			including any publication restrictions	
28				
29				
30				
31				
32	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	NA
33	authorship		professional writers	
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	NA
37	reproducible		participant-level dataset, and statistical code	
38	research			
39				
40				
41	Informed consent	#32	Model consent form and other related documentation given	NA
42	materials		to participants and authorised surrogates	
43				
44				
45	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA
46			biological specimens for genetic or molecular analysis in the	
47			current trial and for future use in ancillary studies, if	
48			applicable	
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 54 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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