UNIVERSIDAD DE COLIMA

SCHOOL OF MEDICINE

MASTER OF MEDICAL SCIENCES

RESEARCH PROTOCOL

EFFECT OF TRIMEBUTINE AND PROBIOTICS ON FUNCTIONAL ABDOMINAL PAIN IN CHILDREN: RANDOMIZED CLINICAL TRIAL

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ABSTRACT:

Objective: To evaluate the efficacy of trimebutine and probiotics in Functional Abdominal Pain Disorders (FAPD) in children. Introduction: FAPD are common in children and lack well-researched treatments. Their etiology is multifactorial, involving both medical and psychosocial factors. Materials and methods: A double-blind, randomized clinical trial will be conducted with 82 children aged 4 to 18 years. Participants will be assigned to one of three groups: trimebutine/probiotics, probiotics/placebo, or trimebutine/placebo. Measurements will be taken at baseline, 4 weeks, and 8 weeks. Results: … Discussion: …

KEYWORDS:

Randomized clinical trial, placebo, double-blind, abdominal pain, trimebutine, probiotics, lactobacillus rhamnosus GG.

INTRODUCTION

Functional Gastrointestinal Disorders (FGID) represent a set of diseases that affect the gastrointestinal (GI) system without a present organic cause, they are characterized by chronic or recurrent symptoms such as abdominal pain, abdominal distension, changes in bowel habits and bowel movement dysfunction. (1,2).

Within the FGID, there are Functional Abdominal Pain Disorders (FAPD) where abdominal pain is the common symptom, present in the pediatric population, and with a prevalence that can vary depending on age, gender and geographic region, affecting approximately one in four children and adolescents, with a higher prevalence in Latin America(3).

The etiology of FGID and FAPD is complex and multifactorial, involving the interaction of genetic, environmental and psychosocial factors. At a pathophysiological level, they may be related to alterations in the motility of the GI system, visceral hypersensitivity, alterations in the intestinal barrier and changes in the communication between the central nervous system and the enteric nervous system(4,5).

The management of FAPD is individualized and multidisciplinary, including changes in diet, pharmacological and psychological therapies(6,7). Among pharmacological therapies, trimebutine, a modulator of intestinal motility, has been shown to be effective in reducing abdominal pain and stool frequency in children with irritable bowel syndrome (IBS)(8). On the other hand, probiotics have shown beneficial effects in the treatment of FAPD in pediatric patients(9).

Despite the high prevalence of FGID and FAPD in the pediatric population, research on these disorders at a global and national level is scarce, so it is necessary to investigate effective treatments for this population, which is why it is proposes the following thesis work, which aims to evaluate the effectiveness of trimebutine and probiotics in the treatment of FAPD in pediatric patients.

THEORETICAL FRAMEWORK

1. Abdominal pain in the pediatric patient

Abdominal pain is a common symptom in children. Due to evolution, the pain can be acute or recurrent. Acute abdominal pain can be due to both gastrointestinal and extraintestinal causes; Recurrent abdominal pain can be due to various causes, but only 5 to 10% of cases are of organic origin, while the majority are due to some functional disorder(1). A meta-analysis by Korterink et al. found that the global prevalence of recurrent abdominal pain in children in Western countries is 13.5%(2). The prevalence of abdominal pain can vary depending on age, gender and geographical region, being more common in girls and school-age boys(10).

In the case of functional gastrointestinal disorders (FGID), it is believed that alteration in the motor function of the gastrointestinal tract, visceral hypersensitivity, and dysfunction in communication between the central nervous system and the enteric nervous system may contribute to abdominal pain (eleven).

2. Functional Gastrointestinal Disorders (FGID)

2.1. Definition

Functional gastrointestinal disorders (FGID) are a group of diseases that affect the gastrointestinal (GI) system and have no identifiable organic cause. These conditions are characterized by chronic or recurrent symptoms, such as abdominal pain, bloating, changes in bowel habits, and bowel movement dysfunction. FGIDs are common in the pediatric population and can affect the quality of life of children and their families(2).

2.2. Epidemiology:

FGIDs frequently affect children and adolescents around the world; it is estimated that up to 20% of school-aged children experience symptoms related to FGIDs, although rates vary depending on the population and study methodology(12). Some studies have reported prevalence rates of up to 50%, in specific populations of children with chronic abdominal symptoms(13). FGIDs have been shown to be more common in girls than in boys and tend to increase in prevalence with age. Risk factors for developing FGID include a family history of functional GI disorders, history of GI infections, psychosocial factors such as stress and anxiety, as well as early exposure to adverse life events(14).

23. Etiology:

The etiology of FGID is complex and multifactorial; it is believed to involve an interaction between genetic, environmental and psychosocial factors. At a pathophysiological level, FGIDs may be related to alterations in the motility of the GI system, visceral sensitivity, intestinal barrier function and communication between the central nervous system and the enteric nervous system(5).

Studies have identified multiple factors that may contribute to the development of FGID in children, including genetic predisposition, gut microbiota dysbiosis, low-grade inflammation, alterations in the secretion and absorption of fluids and electrolytes in the intestine, and abnormalities in the function of the enteric nervous system and in pain modulation(15).

2.4. Classification:

FGIDs are classified according to the Rome IV pediatric criteria, classified according to age; in children under five years of age (neonates and young children) such as infant regurgitation, rumination syndrome, cyclic vomiting syndrome, infant colic, functional diarrhea, infant dyschezia and functional constipation; and in patients 5 to 18 years (older child and adolescent) as cyclic vomiting syndrome, functional nausea and vomiting, rumination syndrome, aerophagia, functional dyspepsia, irritable bowel syndrome, abdominal migraine, functional abdominal pain not otherwise specified , functional constipation and non-retentive fecal incontinence, as seen in the following Table 1(16,17).

Table 1. GFR according to Rome IV Pediatric Criteria

Neonate and young child (< 5 years)		**Older child and adolescent (4 to 18 years)**	
G1	Infant regurgitation	H1	Functional nausea and vomiting disorders
G2	Rumination syndrome	H1a	Cyclic vomiting syndrome
G3	Cyclic vomiting syndrome	H1b	Functional nausea and vomiting
G4	Infant colic	H1c	Rumination syndrome
G5	Functional diarrhea	H1d	Aerophagia
G6	Infant dyschezia	**H2**	**Functional abdominal pain disorders (FAPD)**
G7	Functional constipation	H2a	Functional dyspepsia

H2b	Irritable bowel syndrome (IBS)
H2c	abdominal migraine
h2d	Functional abdominal pain not otherwise specified
H3	Functional defecation disorders
H3a	Functional constipation
H3b	Non-retentive fecal incontinence

* Adapted from Blesa-Baviera, 2017[17].

3. Functional Abdominal Pain Disorders (FAPD)

3.1. Definition

Functional abdominal pain disorders (FAPD) in children and adolescents are a group of disorders in which patients experience abdominal pain without an apparent organic cause. These disorders fall under the general classification of functional gastrointestinal disorders (FGID) and are based on the Rome IV diagnostic criteria(10,12). FAPDs include functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and abdominal pain not otherwise specified (FAD-NEOM)(18).

3.2. Epidemiology

The prevalence of FAPD varies depending on the population studied and the diagnostic criteria used. According to the Rome IV criteria, the global prevalence of FAPD in children and adolescents ranges between 13.5% and 20.7%(2,19). IBS is the most common, with a prevalence of 8.8%, followed by FD with a prevalence of 5.8% and FAP-NOS with a prevalence of 1.1%(2). FDAD are more common in girls than in boys and tend to be more frequent during adolescence(19,20).

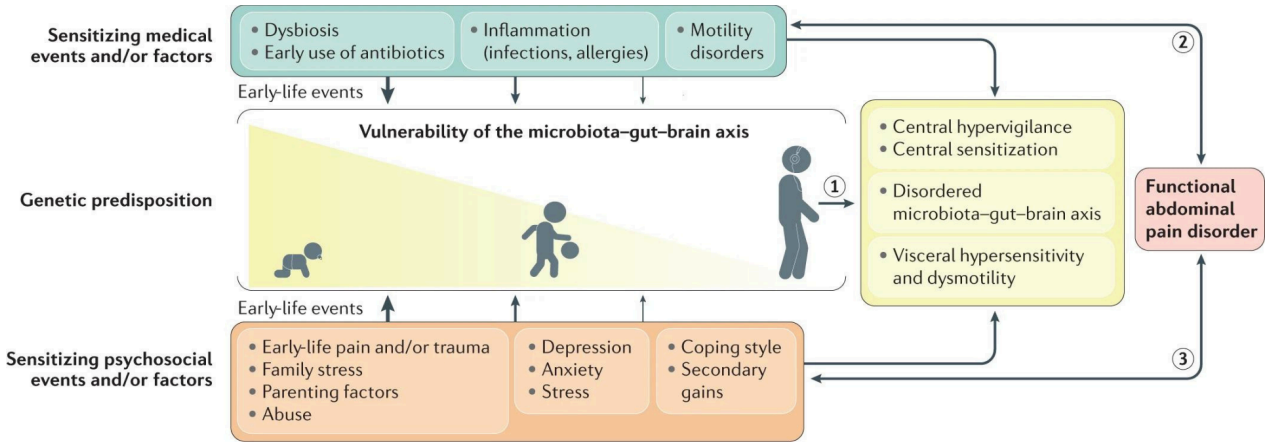
3.3. Etiology

The etiology of FAPD is multifactorial and may involve genetic, environmental, psychological and pathophysiological factors. Alterations in the motor function of the gastrointestinal tract, visceral perception, and intestinal barrier function have been identified in patients with FAPD. Psychological factors, such as stress and anxiety, can also influence the onset and course of FAPD(4,21).

3.4. Pathophysiology

Visceral hyperalgesia leading to disability is shown to be the end result of sensitizing medical factors overlaid on a background of genetic predisposition and early life events (Figure 1)(5).

Figure 1. Etiopathogenesis and summary pathophysiology of FAPD.



*Adapted from Thapar, et al., 2020[5].

3.5. Classification and diagnosis (Rome IV Criteria)

FAPD are classified according to the Rome IV criteria into four main subtypes with diagnostic criteria as seen in Table 2(5,16):

Table 2. Diagnostic Criteria for Functional Abdominal Pain Disorders (FAPD)	
H2a. Functional dyspepsia (FD)	You must have one or more of the following symptoms at least four days a month, for at least two months prior to diagnosis: 1. Postprandial fullness. 2. Early satiety. 3. Epigastric pain or heartburn not associated with defecation. 4. After appropriate medical evaluation, the symptoms cannot be attributed to another condition.
H2b. Irritable bowel syndrome (IBS)	You must meet all of the following: 1. Abdominal pain at least four days per month associated with one or more of the following, for at least two months prior to diagnosis: a. Related to defecation. b. Changes in defecation frequency. c. Changes in the shape or appearance of bowel movements.

	2. In children with constipation, the pain does not resolve with its resolution. 3. After appropriate medical evaluation, the symptoms cannot be attributed to another condition. **Subtypes:**IBS with constipation, IBS with diarrhea, IBS with constipation and diarrhea, undefined IBS.
H2c. Abdominal migraine (AM)	You must do all of the following at least twice in the six months before diagnosis: 1. Paroxysmal episodes of periumbilical, midline or diffuse abdominal pain, lasting an hour or more, this being the most important symptom. 2. Episodes separated by weeks to months. 3. The pain is disabling and interferes with normal activity. 4. Symptoms and stereotyped patterns in each individual patient. 5. The pain is associated with two or more of the following: anorexia, nausea, vomiting, headache, photophobia, and paleness. 6. After appropriate medical evaluation, the symptoms cannot be attributed to another condition.
H2d. Abdominal pain not otherwise specified (FAD-NEOM)	You must do all of the following at least 4 times a month for at least 2 months prior to diagnosis: 1. Episodic or continuous abdominal pain that does not occur only during physiological events (e.g., eating, menstruation). 2. Insufficient criteria for IBS, DF or MA. 3. After appropriate medical evaluation, the symptoms cannot be attributed to another condition

*Adapted from Menninga, et al., 2016[16].

In the diagnostic approach to functional abdominal pain disorders, it is important to identify the presence of alarm data, which can guide us to an organic origin of abdominal pain (Table 3)(1).

Table 3. Warning signs and symptoms in children with recurrent abdominal pain.
Family history of inflammatory bowel disease, celiac disease, or peptic ulcer
Persistent pain in the right upper or right lower quadrant
Dysphagia
Odynophagia
Persistent vomiting
gastrointestinal bleeding
nocturnal diarrhea
Arthritis
Perianal disease
Unintentional weight loss

Growth arrest Delayed puberty Unexplained fever

* Adapted from Sánchez-Ramírez, 2023[1].

3.6. Treatment

The management of FAPD is multidisciplinary and individualized, since the effectiveness of interventions can vary between patients. Treatment may include changes in diet, pharmacological therapies and psychological therapies(6,7).

1. Changes in the diet: inclusion of fiber, reduction in fat intake and the implementation of a diet low in FODMAPs (Fermentable Oligo-, Di-, Monosaccharides and Polyols)(22,23).
2. Pharmacological therapies: antispasmodics (trimebutine), tricyclic antidepressants, probiotics and laxatives to treat the symptoms of FAPD(24,25).
3. Psychological therapies: cognitive-behavioral therapy, hypnotherapy and relaxation therapy, can be beneficial in the management of FAPD, especially in patients with psychological factors that contribute to their symptoms(26,27).

4. Trimebutine in the treatment of Functional Abdominal Pain Disorders (FAPD)

4.1. Pharmacokinetics

Trimebutine is a drug with variable oral bioavailability, ranging from 30% to 100%. After oral administration, it is rapidly absorbed from the gastrointestinal tract and reaches its maximum plasma concentration in approximately 1-2 hours. Trimebutine is primarily metabolized in the liver, and its metabolites are excreted via the kidneys and bile. The elimination half-life of trimebutine is approximately 6 hours, allowing it to be administered in multiple doses throughout the day. As a general rule, a dose of 10-15 mg/kg/day, divided into 2 or 3 doses per day, has been suggested(28).

4.2. Pharmacodynamics

Trimebutine is a gastrointestinal motility modulator that acts on μ-, κ-, and δ-opioid receptors, primarily in the gastrointestinal tract. Trimebutine also interacts with calcium and potassium channels in intestinal smooth muscle cells, contributing to its motility-regulating

action. In addition, trimebutine has an antispasmodic effect on gastrointestinal smooth muscle and improves the coordination of peristalsis in the intestine, which may be useful in the treatment of functional abdominal pain and other gastrointestinal disorders(29).

4.3. Clinical trials

There are few studies evaluating the effects of trimebutine and FAPDs; a double-blind, placebo-controlled study showed that trimebutine was effective in reducing abdominal pain and stool frequency in children with irritable bowel syndrome (IBS)(8). A prospective study showed that trimebutine significantly relieved abdominal pain and improved quality of life in children with functional dyspepsia(30). Furthermore, it was found that trimebutine was effective in the treatment of functional constipation in children, improving the frequency of bowel movements and reducing abdominal pain(31).

5. Effect of probiotics in the treatment of Functional Abdominal Pain Disorders (FAPD)

5.1. Pharmacokinetics and pharmacodynamics

Probiotics are live microorganisms that, when administered in adequate quantities, provide health benefits to the host(32). The pharmacokinetics and pharmacodynamics of probiotics vary widely depending on the strain used, the dose, and the mode of administration. Probiotics are generally not absorbed systemically and exert their effects locally in the gastrointestinal tract. Probiotics can interact with the intestinal microbiota, intestinal mucosa and the immune system, which can lead to changes in gastrointestinal function, inflammation and immunity(33).

Changes in the intestinal microbiota can occur through modification in function, composition (dysbiosis) or interactions between the microbiota and the host. These changes develop in the first years of life, reaching a stable microbial population in the second year and a profile similar to the adult around 4 years old. The use of probiotics could improve the intestinal microbial population, increase mucus secretion, and prevent the destruction of tight junction proteins by decreasing the number of lipopolysaccharides (LPS). When LPS binds to endothelial cells with toll-like receptors (TLR 2, 4), dendritic cells (DCs) and macrophages are activated, and inflammatory markers are increased. Additionally, a decrease in gut dysbiosis and gut leakage following probiotic therapy may minimize the development of inflammatory biomarkers and attenuate unnecessary

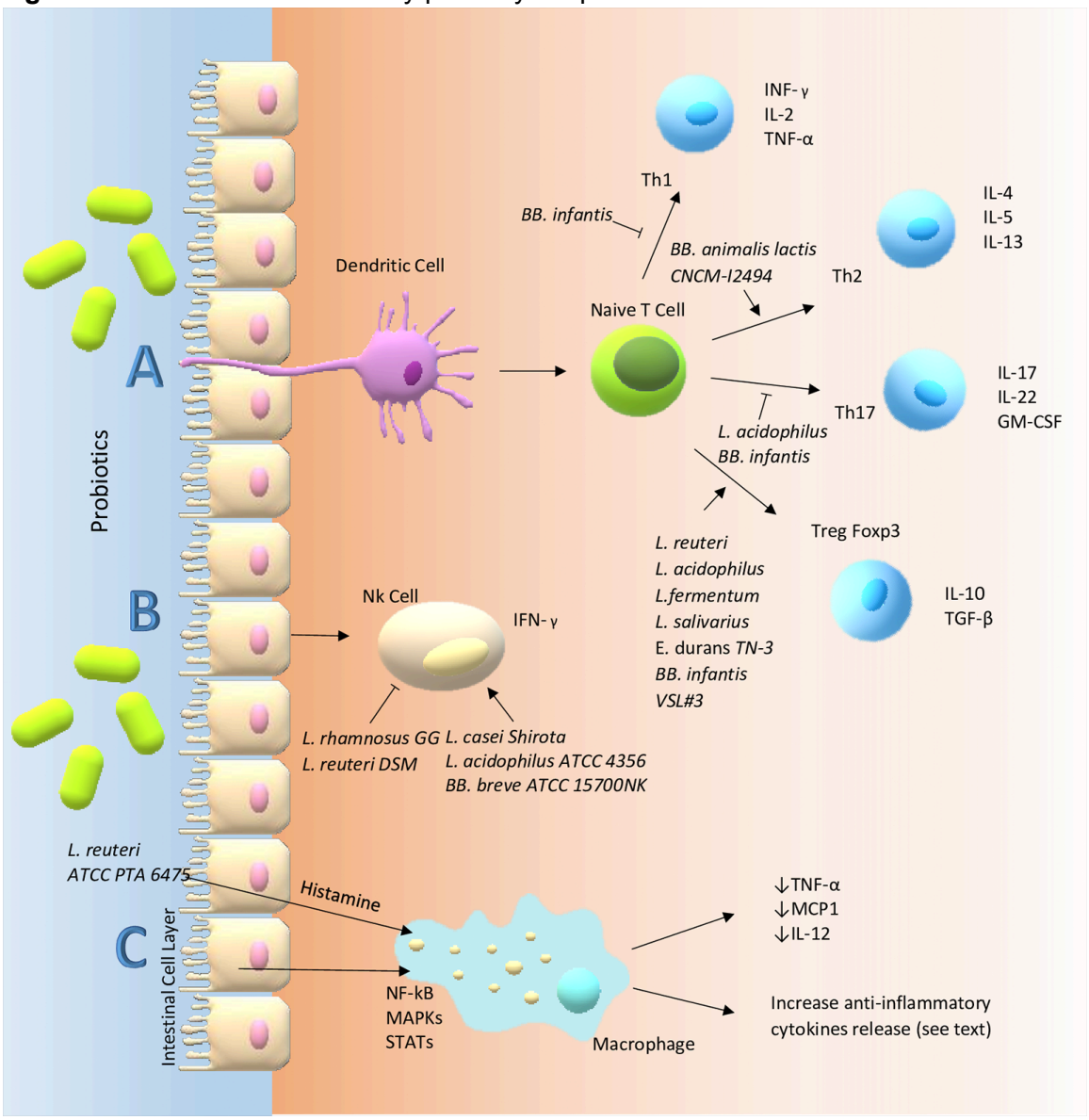
activation of the immune system. In turn, probiotics enhance the differentiation of T cells against Th2 and the development of Th2 cytokines, such as IL-4 and IL-10 (36).

5.2. Probiotic strains and doses for the treatment of FAPD in pediatrics

Studies have shown that certain strains of probiotics may be effective in treating functional abdominal pain disorders in pediatric patients. Some probiotic strains that have shown beneficial effects include Lactobacillus rhamnosus GG (LGG), Lactobacillus reuteri DSM 17938, and Bifidobacterium infantis 35624(34–35).

L. rhamnosus HN001 in human intestinal cells interacts with TLR-9 and suppresses the NF-kB inflammatory pathway through inhibition of TLR-4. L. reuteri exerts an anti-inflammatory action, increasing Treg cell activation and IL-10 levels. The overall effect is a significant decrease in the proinflammatory cascade with inhibition of the proliferation of surrounding T cells. Specific strains of probiotics can negatively or positively stimulate NK cells: L. rhamnosus GG and L. reuteri DSM 17938 inhibit the activation of T cells and NK cells and the release of IFN-y. The different interaction between probiotics, DCs and NK cells clearly reveals how each strain can differently modulate the immune system and inflammatory responses; The NK/CD balance is complex and probiotics could be used to exert beneficial effects (Figure 3)(36).

Figure 3. Main immunomodulatory pathways of probiotics in the intestine.



*Adapted from Cristofori, et al., 2021[36].

The effect of probiotics may be mediated by their metabolites, such as short-chain fatty acids (SCFAs), particularly propionate, acetate and butyrate, which may exert anti-inflammatory effects. SCFAs are produced by bifidobacteria, lactobacilli, and various commensal bacteria. These metabolites exert their action by binding to specific receptors on intestinal epithelial cells. In this way, the NF-kB pathway, the suppression of Treg cells and the production of proinflammatory cytokines by neutrophils and macrophages are inhibited; consequently, the inflammatory state is prevented and an anti-inflammatory effect is produced (36).

The effective doses of these probiotics vary, but in general, the doses used in clinical studies range from 1x109 to 3x109 colony-forming units (CFU) per day(37–38). In a meta-analysis carried out by Gordon M., et., on the use of probiotics for the management of FAPD, low evidence was found with an I2 = 70%(9).

JUSTIFICATION

Magnitude

Functional Gastrointestinal Disorders (FGID) are common in children and adolescents, which justifies the need to investigate effective treatments for this population. A recent meta-analysis and systematic review examined the prevalence of FGID in children and adolescents according to the Rome IV criteria, finding an overall prevalence of 23%. The most common disorders were functional constipation (FE) with a prevalence of 12%, followed by functional dyspepsia (FD) (5%) and irritable bowel syndrome (IBS) (3%). The prevalence of FGID was higher in the Americas, with 23.67% (21.2 - 26.2%)(3).

These epidemiological data demonstrate that FGIDs, including Functional Abdominal Pain Disorders (FAPD), are a major concern in pediatric health, affecting approximately one in four children and adolescents. Furthermore, the higher prevalence in the Americas suggests that countries in this region, including Mexico, could especially benefit from additional research in this field.

Transcendence

Research on FAPD in pediatric patients worldwide and nationally is scarce. This is problematic, as the effectiveness and safety of treatments used in adults cannot always be directly extrapolated to children due to differences in physiology and drug metabolism. This lack is even more worrying considering that trimebutine, a medication that could be promising for these disorders, has not yet been studied in depth in the context of FAPD in children. Furthermore, at a time when the use of probiotics is gaining popularity as an adjuvant treatment, it is crucial to evaluate their efficacy and safety in this vulnerable population. Carrying out a clinical trial that investigates the effectiveness of trimebutine and probiotics in the treatment of FAPD in children would be transcendental. This would not only increase the amount of research in Mexico on this topic, but will also provide valuable information on appropriate treatment in children. Additionally, the study results could help doctors make decisions, which could improve the quality of life for affected children and their families.

Feasibility/Viability

There are few studies in children on FAPD, however, some studies have investigated the effectiveness of trimebutine and probiotics in the treatment of FAPD in children.

Conducting the clinical trial is also feasible due to the availability of trimebutine and probiotics on the market and the prevalence of FAPDs in the pediatric population. Furthermore, the design of the randomized clinical trial would allow an effective comparison between the groups treated with trimebutine, probiotics and the control group, which will provide solid and reliable information on the effectiveness of the proposed treatments.

Vulnerability

The implementation of the clinical trial in Colima will offer a valuable opportunity to examine the effectiveness of trimebutine and probiotics in the treatment of FAPD in pediatric patients, however, the compliance of parents with respect to the treatment prescribed by the patient must be taken into account. doctor. Adherence to treatment may be a critical factor in the effectiveness of the intervention and, therefore, it is essential to evaluate it in the context of the study. With the information obtained, strategies could be developed to improve treatment adherence and optimize results in the management of FAPD in the pediatric population.

PROBLEM STATEMENT

ADFTs in the pediatric population represent an insufficiently explored area of research despite their high prevalence, being mainly alarming given that treatments in adults are not necessarily extrapolated to the pediatric population due to differences in physiology and drug metabolism. , so its effectiveness and safety in children have not yet been conclusively established.

Therefore, this study seeks to address these gaps in the literature by evaluating the efficacy of trimebutine compared to probiotics in the treatment of FAPDs in pediatric patients in reducing abdominal pain. The findings could have significant implications in clinical practice by providing empirical data that could guide the treatment of ADD in the pediatric population, improving their quality of life.

METHODOLOGICAL DESIGN

Research question

What is the effect of trimebutine and probiotics on Functional Abdominal Pain Disorders in pediatric patients?

Goals

General

To evaluate the effect of treatment with trimebutine and probiotics in the treatment of Functional Abdominal Pain Disorders (FAPD) in pediatric patients.

Specific

1. To identify the prevalence of Functional Gastrointestinal Disorders (FGID) in pediatric patients according to the Rome IV criteria.
2. To measure the prevalence of Functional Abdominal Pain Disorders (FAPD) in pediatric patients according to the Rome IV criteria.
3. To determine the effectiveness of treatments with trimebutine and probiotics in reducing pain in pediatric patients with FAPD.
4. To evaluate the impact of treatments with trimebutine and probiotics on the quality of life of pediatric patients with FAPD.

5. To assess the safety and tolerability of treatments with trimebutine and probiotics in the treatment of FAPD in pediatric patients.
6. Identify the factors associated with the presentation of FAPD in pediatric patients.

Hypothesis

Hi: The efficacy of treatment with trimebutine is greater against probiotics in the treatment of Functional Abdominal Pain Disorders (FAPD) in pediatric patients.

H0: The efficacy of treatment with trimebutine and probiotics is equal in the treatment of Functional Abdominal Pain Disorders (FAPD) in pediatric patients.

Ha: The effectiveness of probiotic treatment is greater than trimebutine in the treatment of Functional Abdominal Pain Disorders (FAPD) in pediatric patients.

Ha2: There is a greater reduction in pain with combined treatment in Functional Abdominal Pain Disorders (FAPD) in pediatric patients.

Material and methods

Study design

Placebo-controlled, randomized, double-blind clinical trial (patient/legal guardians, principal investigator).

Study universe

Children from 4 to 18 years old who attend pediatric consultation.

Study timing

January to December 2024.

Selection criteria

Inclusion criteria

- Pediatric patients from 4 to 18 years old.
- Meet the Rome IV criteria for any of the Functional Abdominal Pain Disorders (Functional Dyspepsia, IBS, Abdominal Migraine, or Functional Abdominal Pain Not Otherwise Specified)
- Having signed the informed consent by the parents or legal guardians of the minor.

Exclusion criteria

- Patients who present abdominal pain of organic cause.
- Immunosuppressed patients.
- Patients with previous hypersensitivity to the study drug.

Elimination criteria

- Voluntary withdrawal from the study.
- Patients not adherent to treatment (less than 80%)
- Patients who are participating in another study simultaneously.
- Patients who are being treated by another doctor simultaneously.

Variables

Independent variables

Variable	Operational definition	Guy	Scale
Treatment	Patient who received treatment with trimebutine/probiotics, trimebutine/placebo, probiotics/placebo	Qualitative nominal polytomous	Trimebutine/probiotics Trimebutine/placebo Probiotics/placebo

Dependent variables

Variable	Operational definition	Guy	Scale
Functional Abdominal Pain Disorders (FAPD)	Rome IV Criteria	Qualitative nominal polytomous	Functional dyspepsia (FD) Irritable bowel syndrome (IBS) Abdominal migraine (AM) Abdominal pain not otherwise specified (DAF-NEOM)
Abdominal pain intensity	Subjective feeling of discomfort or discomfort in the abdominal region.	Continuous quantitative	4 to 10 years: Wong-Baker Pain Scale 10 to 18 years: Visual analogue scale (VAS) score
Quality of life	State of complete physical, mental and social well-being.	Continuous quantitative	Score obtained 0 - 100 with the PedsQL 4.0 scale (Pediatric Quality of Life Inventory) Generic Core Scales.

Intervening variables

Variable	Operational definition	Guy	Scale
Age	Chronological age in months	Continuous quantitative	48 to 216 months
Sex	Sex corresponding to your phenotype	Dichotomous nominal qualitative	Man Women
Scholarship	Maximum educational level achieved.	Ordinal qualitative	Preschool Primary

			Secondary Baccalaureate
BMI	Measurement of weight in relation to height	Continuous quantitative	WHO percentiles for age.
Medicines	Drugs other than trimebutine and probiotics that could have an impact on gastrointestinal function or the perception of abdominal pain.	Nominal qualitative	List of indicated medications (free text box)

Sampling method

Probabilistic, random, stratified sampling (Irritable Bowel Syndrome, Functional Dyspepsia, Abdominal Migraine and FAD-NEOM) and simple random sampling to form groups A (trimebutine/probiotics), B (trimebutine/placebo) and C (probiotics/placebo).

Evaluation instruments

Rome IV criteria for pediatric patients 4-10 years (See Annex 2); Rome IV criteria for pediatric patients 10-18 years (See Annex 3)(3); PedsQL 3.0 Gastrointestinal Symptoms Module (Appendices 5-7); Weekly medication reports and Visual Analogue Scale (VAS) for those over 10 years of age and the Wong-Baker Faces Scale for children under 10 years of age (Appendixes 8-9).

Study headquarters

Private pediatric consultation (Dr. Carmen Alicia Sánchez Ramírez and associated pediatric doctors)

Sample size

The Fleiss formula was used to calculate the general sample size N, adjusting N for each stratum using its prevalence, taking into account the 4 strata (Irritable Bowel Syndrome, Functional Dyspepsia, Abdominal Migraine and FAD-NOS) with prevalences of 8.8, 5.8, 1.1 and 1.1% respectively, and 3 treatment groups (trimebutine, probiotics and placebo) with efficacy in reducing pain intensity of 94.9 and 50.0%, respectively. (8,9,39).

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2)) \times DEFF}{(p_1 - p_2)^2}$$

$Z_{\alpha/2}$ = 1.96 (for a significance level ofα=0.05)

Z_{β}= 1.64 (for a statistical level of$1-\beta$=0.95)

p1= 0.949 (trimebutine efficacy)

p2= 0.5 (probiotic efficacy)

$DEFF$= 1 (completely randomized design effect)

$$n = \frac{(1.96 + 1.64)^2 \times (0.949(0.051) + 0.5(0.5)) \times 1}{(0.949 - 0.5)^2} = = = \frac{(3.6)^2 \times (0.048399 + 0.25) \times 1}{(0.449)^2} \frac{12.96 \times 0.298399}{0.201601} \frac{3.8722944}{0.201601}$$

n = 19.22 = 20 per treatment group.

The sample size n is adjusted according to the prevalence of each stratum with the formula:$n_i = n \times \frac{w_i}{\sum w_i}$

$n_{SII} = 20 \times \frac{8.8}{16.8}$= 10.48 = 11 x 3 (trimebutine/probiotics, trimebutine/placebo and probiotics/placebo) = 33 20% (additional margin of adherence to treatment) = 40 for the IBS stratum.±

$n_{DF} = 20 \times \frac{5.8}{16.8}$= 6.90 = 7 x 3 = 21 20% = 26 for the DF stratum.±

$n_{MA} = 20 \times \frac{1.1}{16.8}$= 1.31 = 2 x 3 = 6 20% = 8 for the MA stratum.±

$n_{DAF-NEOM} = 20 \times \frac{1.1}{16.8}$= 1.31 = 2 x 3 = 6 20% = 8 for the DAF-NEOM stratum.±

N = 82.

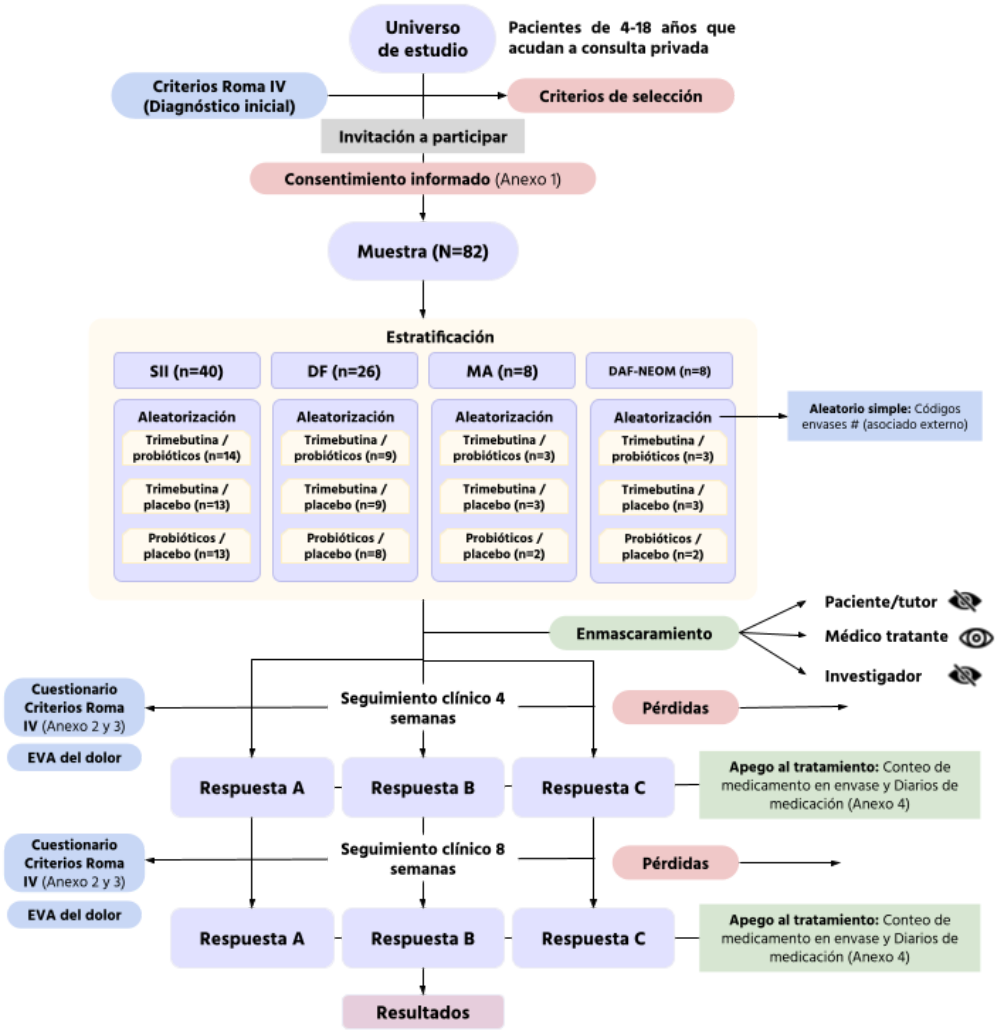
Methodological description

The protocol will be subject to review by the Bioethics Committee of the School of Medicine of the Universidad de Colima, as well as the Research Committee and the Research Ethics Committee of the Hospital Regional Universitario de Colima. Once approval is obtained, a placebo-controlled, randomized, double-blind clinical trial will be carried out, based on the CONSORT guidelines (Annex 11)(40). This trial involves the participation of both pediatric patients aged 4 to 18 years, their legal guardians, their treating physician, and the principal investigator.

Patients will be selected from among those who attend private consultation and who meet the Rome IV criteria for any of the Functional Abdominal Pain Disorders. Patients who meet these criteria will be invited to participate in the study. Before any intervention is performed, the purpose and procedures of the study will be explained to patients and their legal guardians. If they decide to participate, they will be asked to sign a letter of informed consent and the minor's assent. Patients will be selected through probabilistic sampling stratified into 4 (Irritable Bowel Syndrome, Functional Dyspepsia, Abdominal Migraine and FAD-NOS), until the desired sample size of 82 participants is reached. Once the participants are selected, they will be assigned by simple random sampling to one of the three groups: trimebutine/probiotic, probiotic/placebo or trimebutine/placebo, each group consisting of at least 20 participants. The initial diagnosis will be made using the Rome IV Criteria Questionnaires for pediatric patients (Annexes 2-4), the quality of life will be evaluated with PedsQL 3.0 Gastrointestinal Symptoms Module (Annexes 5-7), the intensity of pain with the Scale Visual Analogue (VAS) for those over 10 years of age and the Wong-Baker Faces Scale for children under 10 years of age (Appendixes 8-9). Patients will be prescribed the treatment corresponding to their assigned group and will undergo clinical follow-up at 4 and 8 weeks. During these follow-up consultations, the Rome IV Criteria Questionnaires and scales will be administered again to evaluate the evolution of patients' symptoms, as well as their response to treatment. Any patient who requests voluntary withdrawal, those with less than 80% adherence to treatment (assessed by counting the medication in the container and weekly medication reports, annexes 8-9), and those who are participating in another study or are being treated by another doctor simultaneously.

The data obtained in each consultation (initial, at 4 weeks and at 8 weeks) will be recorded in an Excel spreadsheet for subsequent statistical analysis.

Figure 2. Methodological description



* Own elaboration.

Statistical analysis and data interpretation

The statistical analysis will be carried out using IBM SPSS Statistics 26. Descriptive statistics will be used with measures of central tendency, presenting the results in tables and graphs.

To determine if the data follow a normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests will be applied. The measurements will be analyzed in 3 groups (trimebutine, probiotics and control) and at 3 times (0, 4 and 8 weeks). For the categorical intervening variables such as sex and education, the chi-square test (X2) will be used. For continuous variables such as age and BMI, the Mann-Whitney U test will be applied, expecting statistically significant differences with $p < 0.05$.

If the data follow a normal distribution, repeated measures ANOVA will be used to compare the means of the 3 groups (trimebutine/probiotics, trimebutine/placebo, and probiotics/placebo). The McNemar test or sign test will be taken into account as a secondary analysis to evaluate changes within each group over time (0, 4 and 8 weeks). If the data do not follow a normal distribution, non-parametric tests such as the Friedman test will be used.

If a statistically significant difference is found in repeated measures ANOVA or in the Friedman test, post hoc tests will be performed to identify specific differences between groups and times. If necessary, correlation tests such as Pearson or Spearman will be used to evaluate the relationships between different variables within the study.

ETHICAL CONSIDERATIONS

In accordance with the international principles of Ethics for research on human beings established in the Declaration of Helsinki and the Nuremberg Code. In national documents such as NOM-012-SSA3-2012, the General Health Law in its articles 100 and 101 of chapter V, Research for Health, in the Regulations of the General Health Law on Research for Health (DOF 04-02-2014), where article 17, section I, establishes that this research is classified as research with minimal risk, as it is a research study with commonly used medications, wide therapeutic range, authorized for its sale, using the established indications, doses and routes of administration, which is why informed consent is necessary (Annex 1), a letter of no conflict of interest (Annex 10) and approval by an Ethics and Research Committee will be necessary. .

Furthermore, according to article 15 of the same Regulation, considering a protocol with an experimental design in human beings, which includes several groups, random selection methods will be used to obtain an impartial assignment of the participants in each group and the pertinent measures will be taken to avoid any risk or damage to the research subjects, as well as the privacy of the individual subject of research, identifying themselves only when the results require it and they authorize it as established in article 16 of this same Regulation.

Likewise, it will be carried out in accordance with Chapter III, Research on Minors or Incapacitated Children, respecting articles 34 to 37 of the Regulations of the General Health Law on Health Research, requiring the consent of the minor, when the mental capacity and psychological state of the minor allow it, providing appropriate information for the understanding of the minor, based on this, the research is classified as risky and with the probability of direct benefit for the minor or the incapable, in accordance with article 38, position that the risk is justified by the importance of the benefit that the minor will receive by receiving the treatment, and the benefit is equal to or greater than other alternatives already established for diagnosis and treatment, according to fractions I and II.

This protocol will be submitted for evaluation and approval by the Research Committee and the Research Ethics Committee of the Hospital Regional Universitario de Colima. Likewise, it will be registered in the Clinical Trials database of the US Department of Health and Human Services. The participants and those responsible for the research protocol undertake to safeguard the information confidentially, as well as guarantee the rights of the subjects. study.

FINANCING

Human Resources

1. Principal researcher: Pablo Hernan Sandoval Villaseñor, Master's Student in Medical Sciences, Universidad de Colima.
2. Thesis advisors: Dr. C. Carmen Alicia Sánchez Ramírez, Dr. C. Fabián Rojas Larios.

Physical resources

Resource type	Unit	Amount	Cost per unit	Cost
Computer	Part	1	$0 (Personal use)	$0
EPSON L4150 printer	Part	1	$0 (Personal use)	$0
Black ink for EPSON 504 printer	Part	1	$250	$250
Sheets	Pack of 500 sheets	5	$200	$1000
Pens	Box with 12 pieces	2	$70	$140
Trimebutin tablets 200 mg (Espabion)	Box with 40 tablets	39 (28 tablets per patient, 26 patients, 2 consultations)	$94.0	$3572
Trimebutin suspension 20 mg/ml (Espabion)	Bottle with 100 ml	26 (4 bottles per patient, 13 patients, 2 consult)	$150.0	$3900
Probiotics Lactobacillus rhamnosus GG	Box with 10 envelopes of 1.5 gr	157 (28 envelopes per patient, 28 patients, 2 consultations)	$250 (approx.)	$39250
Placebo	Box with 28 microcrystalline cellulose tablets 8 mm 250 mg.	56 (28 tablets per patient, 28 patients, 2 consultations)	$0 (Faculty of Chemical Sciences)	$0
			Totall	$48,112 MXN

SCHEDULE OF ACTIVITIES

ACTIVITY	PROGRAMMED CALENDAR MONTHS																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. Modifications to the research protocol	■	■	■	■	■	■																		
2. Evaluation and authorization of the protocol by an Ethics and Research Committee							■																	
3. Pilot test of evaluation and informed consent instrument								■																
4. Sample of patients and randomization of study groups (G1 and G2) and control									■	■	■	■	■											
5. Follow-up 4 weeks start of treatment study groups (G1, G2) and control.														■	■	■	■							
6. Follow-up 8 weeks start of treatment study groups (G1, G2) and control																		■	■	■	■			
7. Analysis of results																						■		
8. Writing conclusions and discussion																							■	
9. Dissemination of results, publication of article and obtaining a degree																								■

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ANNEXES

Annex 1. Informed consent.

LETTER OF INFORMED CONSENT

Research project name:EFFECT OF TRIMEBUTINE VS PROBIOTICS ON FUNCTIONAL ABDOMINAL PAIN IN CHILDREN: RANDOMIZED CLINICAL TRIAL

Dear parents:

The main objective of this work is to include all children who come for consultation due to recurrent abdominal pain. If you decide to have your child participate in this research, the staff will:

a) Carry out a general evaluation of your health status.

b) Provide pediatric consultation and provide the appropriate medication if applicable.

c) Take necessary data from the patient for research purposes.

d) Monitor the patient and the effect of the administered medications.

This work consists of evaluating the effectiveness of medications used for Functional Abdominal Pain Disorders in the pediatric population, such as pharmacological therapies such as antispasmodics (trimebutine) or probiotics, using a group of patients with placebo, so you should know that Your child may be given any of these medications, but it will have no impact on their health or well-being.

If your child participates, the highly trained doctors who are consulting you will ask you some questions to know your child's health history and will prescribe one of the medications, which must be administered in the dose, frequency and duration indicated until your subsequent appointment, to re-evaluate your child on the signs and symptoms they have presented during treatment and observe if there has been improvement.

All the information you provide about your child's health will be confidential and if you wish, you may withdraw your child from this study at any time you decide, without this affecting the care that is always provided. has been provided by health services. Medical treatment will be provided by the treating doctor, and in case of damages that warrant it, directly caused by the research and if there are additional expenses, these will be absorbed by the research budget. HOWEVER, WE CANNOT PROMISE THAT YOU. YOU WILL RECEIVE SOME ADDITIONAL BENEFIT FROM YOUR PARTICIPATION IN THIS STUDY.

Children as human beings have rights. By participating in this work, you as a tutor must make use of, among others, the following rights:

1. Be informed of the nature and purpose of this work.
2. Receive a detailed explanation of the procedures that will be performed on your child and any medications used.
3. Receive a description of any reasonable inconvenience or risk that may arise.
4. Receive an explanation of any reasonable benefit that could benefit you.

5. Receive information about any alternative measures, as well as medications or other types of treatments that could be useful for the minor, as well as the relative benefits and risks they entail.
6. Be informed of the treatment options if they are available, if complications occur.
7. That you have the opportunity to ask any questions regarding the work or the procedures involved.
8. Be instructed that acceptance in this research can be withdrawn at any time and without detriment or harm to the minor.
9. Be given a copy of this consent, signed and dated.
10. That you have the opportunity to decide about your acceptance or refusal to participate in this work, without the intervention of any force, fraud, lies, pressure, coercion or undue influence on your decision.

Your signature indicates that you have read and understood the content of this letter, that you have asked the questions you considered appropriate and they have been answered appropriately, that you agree for your child to participate, based on the information received and that you have been given a copy of this consent

_____

Patient's full name

_____

Name of parent or guardian

_____	_____
Signature of parent or guardian	Current date

_____	_____
Witness name 1	Witness name 2

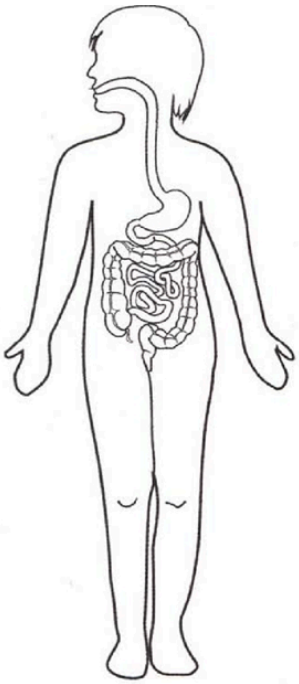
_____	_____
Witness address 1	Witness address 2

Annex 2. Questionnaire for pediatric digestive symptoms, format for parents.

QUESTIONNAIRE FOR PEDIATRIC DIGESTIVE SYMPTOMS, ROME VERSION IV (QPGS-RIV)

(Adapted from the Pediatric Digestive Symptoms Questionnaire, Walker, Caplan-Dover and Rasquin-Weber, 2000)

FORM FOR PARENTS AND REPRESENTATIVES (CHILDREN BETWEEN 4 AND 10 YEARS OF AGE)



Your child's full name	Name of parent or guardian
Date	Signature of parent or guardian

INSTRUCTIONS:

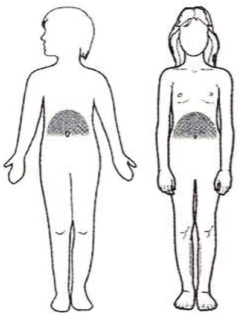
This questionnaire is about the digestive system (esophagus, stomach, small intestine and colon) and problems that your child may have with them. Some problems may exist in your child and others may not.

Please answer all questions to the best of your ability.

If you have any questions, the research staff will be happy to answer them.

Section A.
Pain and discomfort above the navel

The shaded area in the drawing below shows the area above from the navel were some children may feel pain or discomfort. Some terms used to describe the discomfort are: “belly pain”, “nausea”, “bloated belly”, “full belly” or “not being hungry after eating a small amount”.



The questions in this section are about pain or discomfort above the belly button that your child has had in the past month. Children may have pain and discomfort in more than one area of the tummy. In other sections of the questionnaire, we will ask about the areas around or below the belly button.

A1. In the past month, how many days has your child felt pain or discomfort above the navel? (although it didn't last long)
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A2. In the past month, how many days has your child felt burning or burning above the navel? (although it didn't last long)
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A3. In the past month, on how many days has your child felt nauseous or bothered by feeling very full after a normal meal?
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A4. In the past month, how many days was his child not able to finish his meal because he felt too full?

- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

If you answered NEVER to questions 1, 2, 3 and 4, please go to Section B (page 5)

TO 5. When your child feels discomfort or discomfort above the navel (pain, discomfort, burning, fullness, etc.), have they had any of the following discomforts? (You can choose more than one option):

A5a. Stomach more swollen than usual ___ No Yes
A5b. Nausea (feeling like vomiting) ___ No Yes
A5c. Belching ___ No Yes

A6. When your child feels discomfort or discomfort above the navel:

A6a. Does it get worse when eating? ___ No Yes
A6b. Does it improve when eating? ___ No Yes

A7. How long has your child had discomfort or discomfort above the navel (pain, soreness, burning, fullness, etc.)?

- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

A8. In the past month, when your child had pain or discomfort above the belly button, how often did she have it at the same time as pooping?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A9. In the past month, when your child had pain or discomfort above the belly button, how often was his or her poop softer or more liquid than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A10. In the past month, when your child had pain or discomfort above the belly button, how often was his or her poop harder or in chunks than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A11. In the past month, when your child had pain or discomfort above the belly button, how often did she poop more times than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

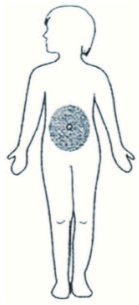
A12. In the past month, when your child had pain or discomfort above the belly button, how often did she poop fewer times than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

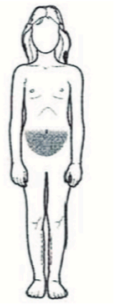
Section b.

Pain and discomfort in the belly button, around the belly button, or below the belly button

The shaded area in the drawing below shows the navel area,around the navel and below the navel were some children may feel pain or discomfort. Sometimes this discomfort is less intense than real pain. Some terms used are: “stomach pain” or “belly pain”.



Alrededor del ombligo



Por debajo del ombligo

B1. In the past month, on how many days did your child feel pain or discomfort in the belly button, around the belly button, or below the belly button?

- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

If you answered NEVER, please go to Section C (page 8)

B2a. Does your child feel pain or discomfort in the navel, around the navel, or below the navel only when he eats or after eating?

- No
- Yeah

B2b. For Girls Only: Do you feel pain or discomfort in your belly button, around your belly button, or below your belly button only when you have your period?

- No
- Yeah
- Her first menstruation has not yet arrived

B3. How long has your child had pain or discomfort in the belly button, around the belly button, or below the belly button?

- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

B4. In the past month, when your child had pain or discomfort in the belly button, around the belly button, or below the belly button, how often did she have it at the same time as pooping?

- Never
- From time to time
- Sometimes

- Most of the time
- Always

B5. In the past month, when your child had pain or discomfort in the belly button, around the belly button, or below the belly button, how often was his or her poop softer or more liquid than normal?

Never
From time to time
Sometimes
Most of the time
Always

B6. In the past month, when your child had pain or discomfort in the belly button, around the belly button, or below the belly button, how often was his or her poop harder or in chunks than normal?

Never
From time to time
Sometimes
Most of the time
Always

B7. In the past month, when your child had pain or discomfort in the belly button, around the belly button, or below the belly button, how often did she poop more times than usual?

Never
From time to time
Sometimes
Most of the time
Always

B8. In the past month, when your child had pain or discomfort in the belly button, around the belly button, or below the belly button, how often did your child poop less than usual?

Never
From time to time
Sometimes
Most of the time
Always

B9. Is your child taking medication for constipation or hard poop?

- No
- Yeah
- I don't know

B9a. If yes, how often does your pain or discomfort in your belly button, around your belly button, or below your belly button get better when you take the medications?

Never
From time to time
Sometimes
Most of the time
Always

B10. Has your child ever had to stop doing the activities she was doing due to very intense abdominal pain around the navel?

- No (if this is your answer, please go to Section C, page 8)
- Yeah

B10a. How long do these episodes of severe abdominal pain last?

- less than 1 hour

- 1-2 hours
- 3-4 hours
- Most of the day
- All day

B10b. In the last 6 months: How often did your child have these episodes of severe abdominal pain?

- 1 time
- 2 times
- 3 to 5 times
- 6 or more times

B10c. During that episode of severe abdominal pain, did your child have any of the following?

1. Lack of appetite ___ No Yes
2. Nausea (feeling like vomiting) ___ No Yes
3. Vomiting ___ No Yes
4. Paleness ___ No Yes
5. Headache ___ No Yes
6. Annoyance with light ___ No Yes

B10d. When severe pain around the belly button is relieved, how long does it take before the severe abdominal pain returns?

- several minutes
- Several hours
- Several days
- Several weeks
- Several months

Section C.

Bowel movements ("poop", "poop", "doing 2")

In this section we will ask about bowel movements. There are many words to define bowel movements: "poop", "poop", "doing 2". Your family can use other words to talk about poop.

C1. In the past month, how often has your child pooped?

- 2 times a week or less
- 3 to 6 times a week
- Once a day
- 2 to 3 times a day
- More than 3 times a day

C2. Look at the scale above and answer: what was your child's poop like last month?

- Type 1
- Type 2
- Type 3
- Type 4
- Type 5
- Type 6
- Type 7
- Variable: not always the same

C2a. If, according to the scale on the previous page, your child's poop is type 1 or type 2, how long has he/she been type 1 or type 2?

- Less than a month
- 1 month
- 2 or more months
- Their poop is usually not hard.

C3. Last month, did it hurt your child's poop? ___ No Yes

C4. In the past month, has your child pooped so big that it clogged the toilet? ___ No Yes

C5. Some people poop despite having a bathroom available. They do this by tensing their bodies or crossing their legs. In the past month, while at home, how often has your child tried to hold in poop?

- Never
- 1 to 3 times a month
- Once a week
- Several times a week
- Every day

C6. Has a doctor or nurse when examining your child told you that she has a lot of poop inside?

- No
- Yeah

C7. In the past month, how often has your child got poop on his/her underwear?

- Never (if you answered never, please go to Section D)
- Less than once a month
- 1 to 3 times a month
- Once a week
- Many times a week
- Every day

C7a. When her son/daughter stained her underwear, how badly did she stain it?

- With pints of poop (not with poop)
- With a small amount of poop (less than a poop)
- With a lot of poop (a complete poop)

C7b. How long has your child stained their underwear?

- less than 1 month
- 1 month
- 2 months
- 3 to 11 months
- One year or more

Section D.
Nausea and vomiting

This section asks about the symptoms of nausea or vomiting. Nausea is when your child feels sick to their stomach or feels like they are going to “take food back.” There are many words for nausea, such as “upset stomach,” “feeling dizzy,” or “being sick to your stomach.” Your family may use a special word when you talk about nausea.

D1. In the past 2 months, how often did your child have nausea or vomiting?
- Never (if you answered never, please go to question 5)
- 1 to 3 times a month.
- Once a week
- 2 times a week
- More than 2 times a week, but not every day.
- Every day

D2. How long has your child felt nauseated or wanted to vomit?
- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

D3. Does nausea start after eating? ___ No Yes

D4. When your child has nausea, he or she has:
1. Vomiting ___ No Yes
2. Belly pain ___ No Yes

4a. If your child has nausea and belly pain at the same time, which one bothers you more?
- Nausea
- Stomachache

The next questions are about vomiting. Vomiting is when food returns to your mouth from your stomach and comes out through your mouth. There may be other ways to call vomiting and your family may call it differently.

D5. In the past month, how often did your child vomit?
- Never (if you answered never, please go to question 8)
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

D6. How long has your child been vomiting?
- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

D7. Does your child ever force himself to vomit (for example, by sticking a finger down his throat)?
- Never
- From time to time
- Sometimes

- Many times
- Always

D8. In the last 6 months: How many times did your child vomit continuously (“non-stop”) for 2 or more hours?
- Never (if you answered never, please go to question 8)
- Once
- 2 times
- 3 times
- 4 or more times

D8a. How long has your child had these episodes of frequent vomiting (“that doesn't stop”)?
- A month or less
- 2 - 3 months
- 4 - 5 months
- 6 or more months

D8b. When your child vomits often (“it doesn't stop”), does she feel nauseous, feel sick to her stomach, or feel like vomiting?
- No
- Yeah

D8c. When that episode of continuous vomiting stops, how long does it take before this continuous vomiting (“that doesn't stop”) is repeated?
- several minutes
- Several days
- Several weeks
- Several months

D9. In the past month, how often did your child put food back in his/her mouth after eating?
- Never (if you answered never, please continue to Section E)
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

D9a. If food comes back into your mouth, does it happen within the first hour after eating?
___ No Yes

D9b. Does food return to your mouth when you are sleeping?
___ No Yes

D9c. Do you usually feel nauseous or vomit when you put food back in your child's mouth?
___ No Yes

D9d. What does your child usually do when food is returned to his or her mouth?
___ Swallows it ___ Spits it out

Section E.
Other symptoms

E1. In the last 2 months, without trying on purpose, how often has your child burped over and over again?
- Never
- 1 to 3 times a month

- Once a week
- Many times per week
- Every day

E2. In the last 2 months, how often did your child fart a lot?
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

E3. In the past 2 months, how often did your child have a larger than normal belly during the day?
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

E4. In the past 2 months, how often has your child swallowed more air than normal? (You may or may not hear noise when swallowing.)
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

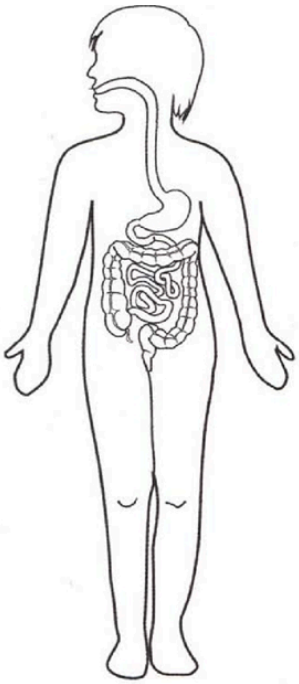
Thank you so much!

Annex 3. Questionnaire for pediatric digestive symptoms, self-report.

QUESTIONNAIRE FOR PEDIATRIC DIGESTIVE SYMPTOMS, ROME VERSION IV (QPGS-RIV)

(Adapted from the Pediatric Digestive Symptoms Questionnaire, Walker, Caplan-Dover and Rasquin-Weber, 2000)

FORMAT FOR CHILDREN AND TEENAGERS (10 YEARS OF AGE AND OLDER)



Your full name	Name of parent or guardian
Date	Signature of parent or guardian

INSTRUCTIONS:

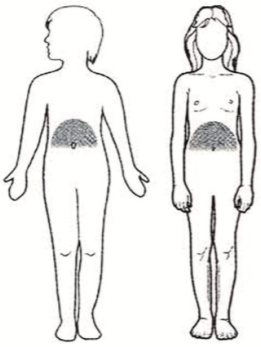
This questionnaire is about your digestive system (esophagus, stomach, small intestine and colon) and problems you may have with it. You may have some problems and not others.

Please answer all questions to the best of your ability.

If you have any questions, the research staff will be happy to answer you.

Section A.
Pain and discomfort above the navel

The shaded area in the drawing below shows the area above the belly button where some children may feel pain or discomfort. Some terms used to describe the discomfort are: “tummy pain”, “tummy pain”, “nausea”, “swollen belly”, “full belly” or “not being hungry after eating a small amount”.



The questions in this section are about pain and discomfort above the navel that you have had in the past month. Children may have pain and discomfort in more than one area of the belly. In other sections of the questionnaire, we will ask you about the areas around or below the belly button.

A1. In the past month, how many days have you felt pain or discomfort above your belly button? (although it didn't last long).
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A2. In the past month, how many days have you felt burning or burning above your navel? (although it didn't last long).
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A3. In the past month, after a normal meal, how many days have you felt very full or nauseous or with your belly more swollen than usual?
- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

A4. In the past month, how many days were you not able to finish your meal because you felt too full?

- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

If you answered NEVER to questions 1, 2, 3 or 4, please go to Section B (page 5)

TO 5. When you feel discomfort or discomfort above the navel (pain, discomfort, burning, fullness, etc.), have you had any of the following discomforts? (You can choose more than one opcion):

to. Belly more inflated than usual ___ No Yes
b. Nausea (feeling like vomiting) ___ No Yes
c. Belching ___ No Yes

A6. When you feel discomfort or discomfort above the navel:

to. Does it get worse when eating? ___ No Yes
b. Does it improve when eating? ___ No Yes

A7. How long have you had discomfort or discomfort above your belly button (pain, soreness, burning, fullness, etc.)?

- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

A8. In the past month, when you had pain or discomfort above your belly button, how often did you have it at the same time as pooping?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A9. In the past month, when you had pain or discomfort above your belly button, how often was your poop softer or more liquid than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A10. In the past month, when you had pain or discomfort above your belly button, how often was your poop harder or in chunks than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

A11. In the past month, when you had pain or discomfort above your belly button, how often did you poop more times than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

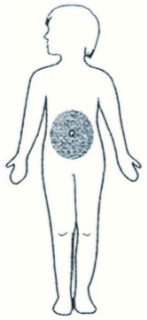
A12. In the past month, when you had pain or discomfort above your belly button, how often did you poop fewer times than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

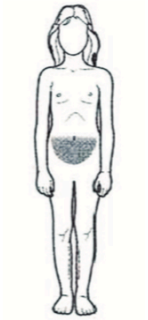
Section b.

Pain and discomfort in the belly button, around the belly button, or below the belly button

The shaded area in the drawing below shows the area of the belly button, around the belly button, and below the belly button where some people may feel pain or discomfort. Sometimes this discomfort is less intense than real pain. Some terms used are: “stomach pain” or “belly pain”.



Alrededor del ombligo



Por debajo del ombligo

B1. In the past month, on how many days did you feel pain or discomfort in your belly button, around your belly button, or below your belly button?

- Never
- 1 day
- 2 days
- 3 days
- 4 days
- 5 or more days

If you answered NEVER, please go to Section C (page 8)

B2a. Do you feel pain or discomfort in your belly button, around your belly button, or below your belly button only when you eat or after eating?

- No
- Yeah

B2b. For Girls Only: Do you feel pain or discomfort in your belly button, around your belly button, or below your belly button only when you have your period?

- No
- Yeah
- I haven't gotten my first period yet.

B3. How long have you had pain or discomfort in your belly button, around your belly button, or below your belly button?

- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

B4. In the past month, when you had pain or discomfort in your belly button, around your belly button, or below your belly button, how often did you have it at the same time as pooping?

- Never

- From time to time
- Sometimes
- Most of the time
- Always

B5. In the past month, when you had pain or discomfort in your belly button, around your belly button, or below your belly button, how often was your poop softer or more liquid than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

B6. In the past month, when you had pain or discomfort in your belly button, around your belly button, or below your belly button, how often was your poop harder or in chunks than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

B7. In the past month, when you had pain or discomfort in your belly button, around your belly button, or below your belly button, how often did you poop more times than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

B8. In the past month, when you had pain or discomfort in your belly button, around your belly button, or below your belly button, how often did you poop less than usual?

- Never
- From time to time
- Sometimes
- Most of the time
- Always

B9. Are you taking medication for constipation or hard poop?

- No
- Yeah
- I don't know

B9a. If yes, how often does your pain or discomfort in your belly button, around your belly button, or below your belly button get better when you take the medications?

Never
From time to time
Sometimes
Most of the time
Always

B10. Have you ever, due to severe abdominal pain around the navel, had to stop doing the activities you were doing?

- No (if this is your answer, please go to Section C, page 8)
- Yeah

B10a. How long does this intense abdominal pain last because you stopped the activities you were doing?

- less than 1 hour
- 1-2 hours
- 3-4 hours
- Most of the day
- All day

B10b. In the last 6 months: How often does that intense abdominal pain occur due to which you stopped the activities you were doing?

- 1 time
- 2 times
- 3 to 5 times
- 6 or more times

B10c. During that episode of severe abdominal pain, did you have any of the following?

1. Lack of appetite ___ No Yes
2. Nausea (feeling like vomiting) ___ No Yes
3. Vomiting ___ No Yes
4. Paleness ___ No Yes
5. Headache ___ No Yes
6. Annoyance with light ___ No Yes

B10d. When the severe pain around the belly button passes, how long does it take before that severe abdominal pain recurs?

- several minutes
- Several hours
- Several days
- Several weeks
- Several months

Section C.
Bowel movements ("poop", "poop", "doing 2")

In this section we will ask about bowel movements. There are many words to define bowel movements: "poop", "poop", "doing 2". Your family can use other words to talk about poop.

C1. In the past month, how often have you pooped?

- 2 times a week or less
- 3 to 6 times a week
- Once a day
- 2 to 3 times a day
- More than 3 times a day

C2. Look at the scale above and answer: What was your poop like in the last month?

- Type 1
- Type 2
- Type 3
- Type 4
- Type 5
- Type 6
- Type 7
- Variable: not always the same

C2a. If according to the scale on the previous page, your poop is type 1 or type 2, how long has it been type 1 or type 2?

- Less than a month
- 1 month
- 2 or more months
- My poop is usually not hard.

C3. Last month, did it hurt when you pooped? ___ No Yes

C4. In the past month, have you had poop so big that it clogged the toilet? ___ No Yes

C5. Some children hold in poop despite having a bathroom available. They do this by tensing up or crossing their legs. In the past month, while at home, how often did you try to hold back pooping?

- Never
- 1 to 3 times a month

- Once a week
- Several times a week
- Every day

C6. Has a doctor or nurse examined you and said that you have a lot of poop inside?

- No
- Yeah

C7. In the past month, how often have you gotten poop on your underwear?

- Never (if you answered NEVER, please go to Section D, page 10)
- Less than once a month
- 1 to 3 times a month
- Once a week
- Many times a week
- Every day

C7a. When you have stained your underwear, how much have you stained it?

- With pints of poop (not with poop)
- With a small amount of poop (less than a poop)
- With a lot of poop (a complete poop)

C7b. How long have you been staining your underwear?

- less than 1 month
- 1 month
- 2 months
- 3 to 11 months
- One year or more

Section D.
Nausea and vomiting

The next questions are about nausea. Nausea is that feeling of wanting to vomit. There are several ways to refer to "nausea," such as feeling sick to your stomach, feeling dizzy, and having a stomach ache. Your family may use other words for nausea.

D1. In the past two months, how often did you feel nauseated or feel like vomiting?
- Never (if you answered NEVER, please continue to question D5)
- Less than once a month
- 1 to 3 times a month
- Once a week
- Many times a week
- Every day

D2. Since when do you feel nauseated or feel like vomiting?
- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

D3. Does nausea start after eating? ___ No Yes

D4. When you have nausea, you have:
1. Vomiting ___ No Yes
2. Belly pain ___ No Yes

D4a. If you have nausea and belly pain at the same time, which one bothers you more?
- Nausea
- Stomachache

The next questions are about vomiting. Vomiting is when food returns to your mouth from your stomach and comes out through your mouth. There may be other ways to call vomiting and your family may call it differently.

D5. In the past month, how often did you vomit?
- Never (if you answered NEVER, please continue to question D8)
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

D6. Since when have you been vomiting?
- A month or less
- 2 months
- 3 months
- 4 to 11 months
- One year or more

D7. Do you ever force yourself to vomit (for example, by putting your fingers in your mouth to make yourself vomit)?
- Never
- From time to time
- Sometimes
- Many times

- Always

D8. In the last 6 months: How many times did you have continuous vomiting (“that doesn't stop”) for 2 or more hours?

- Never (if you answered NEVER, please go to question D9)
- Once
- 2 times
- 3 times
- 4 or more times

D8a. How long have you been having these episodes of frequent vomiting (“that doesn't stop”)?

- A month or less
- 2 - 3 months
- 4 - 5 months
- 6 or more months

D8b. When you vomit frequently (“that doesn't stop”), do you feel nauseated or feel like vomiting?

- No
- Yeah

D8c. When that episode of vomiting stops, how long does it take before it happens again?

- several minutes
- Several days
- Several weeks
- Several months

D9. In the past month, how often did food return to your mouth after eating?

- Never (if you answered NEVER, please continue to Section E, page 12)
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

D9a. If food comes back into your mouth, does this usually happen within the first hour after eating?
___ No Yes

D9b. Does food return to your mouth when you are sleeping?
___ No Yes

D9c. Do you usually feel nauseous or vomit when food is returned to your mouth?
___ No Yes

D9d. What do you usually do when food is returned to your mouth?
___ You swallow it ___ You spit it out

Section E.
Other symptoms

E1. In the past two months, how often did you accidentally burp over and over again?
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

2. In the past two months, how often did you fart a lot?
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

3. In the past two months, how often did your belly feel more swollen than usual during the day?
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

4. In the past two months, how often did you swallow more air than usual? (you may or may not hear noise when swallowing)
- Never
- 1 to 3 times a month
- Once a week
- Many times per week
- Every day

Thank you so much!

Annex 4. Scoring instructions for the Questionnaire for Pediatric Digestive Symptoms, Rome Version IV (QPGS-RIV).

H2. Abdominal pain disorders

H2a. Abdominal dyspepsia: Functional dyspepsia is diagnosed if the child qualifies for postprandial distress syndrome or epigastric pain syndrome or both.

H2a1. Postprandial distress syndrome

- (A3) Fullness "4 days a month" or more often, OR
- (A4) Satiety "4 days a month" or “more often”, AND
- (A7) The duration of pain or discomfort in the upper abdomen is "2 months" or more.

H2a2. Epigastric pain syndrome

- (A1) upper abdominal pain “4 days a month” or “more often,” OR
- (A2) heartburn "4 days a month" or “more often”, AND
- (A7) The duration of pain or discomfort in the upper abdomen is "2 months" or more, AND
- (A8) Not related to a bowel movement: "Never" or "Once in a while", AND
- (A9-12) Not associated with changes in stool form or frequency: "Never or "Occasionally"

H2b. Irritable bowel syndrome

- (B1 or A1) Abdominal pain "4 days a month” or more frequently, AND
- (B3 or A7) Abdominal pain lasts "2 months" or longer, AND
- (B2a) Not exclusively associated with eating ("No"), AND
- (B2b) For girls, not exclusively associated with menstruation ("No" or "Not applicable"), AND
- [At least one (A8-A12) or (B4-B8) intestinal symptoms "Sometimes" or more frequently], AND
- (B9) For those who use laxatives (B9 is “Yes”), the question (B9a) Elimination of symptoms with laxatives should be answered “Never”, “Once in a while” or “Sometimes” (i.e. NO answered “The most of the time" or "Always").

H2c. abdominal migraine

- (B10) Severe pain causing restriction in daily activities ("Yes"), AND
- (B10a) The pain lasts 1 hour or more, AND
- (B10b) In the last 6 months, 2 or more episodes of severe pain, AND
- (B10c) Two or more of the following during pain episodes:
    - No appetite, Ó
    - Nausea, OR
    - Vomiting, OR
    - Pale skin, Ó
    - Headache, OR
    - Light sensitive eyes
- (B10d) Pain episodes are separated by several weeks or more.

H2d. Abdominal pain not otherwise specified (FAD-NEOM)

- Lower abdominal location
    - (B1 or A1) Abdominal pain "4 days a month" or “more often”, AND
    - (B3 OR A7) Abdominal pain lasts "2 months" or longer, AND
    - (B2a) The pain is not exclusively associated with eating ("No"), AND
    - (B2b) In girls, pain is not exclusively associated with menstruation ("No" or "Not applicable"), AND
- Does not meet criteria for other functional gastrointestinal disorders associated with abdominal pain (e.g., functional dyspepsia, IBS, abdominal migraine).

Annex 5. PedsQL 3.0 - Gastrointestinal Symptoms Module. Report from parents of young children

Name:_____

Date:_____ / _____ / _____

PedsQLTM

Gastrointestinal Symptoms Module

Version 3.0

REPORT FROM PARENTS OF YOUNG CHILDREN (ages 5-7)

INSTRUCTIONS

On the next page is a list of things that could be a problem for your child.

Please tell us, by circling each answer, how much of a problem each thing has been for your child in the last month:

0If it's never a problem

1Yes it is almost never a problem

2Yes sometimes it is a problem

3Yes it is often a problem

4Yes it is almost always a problem

There are not correct or incorrect answers.

If you do not understand any question, please ask for help.

In the last month, how much of a problem has this been for your child…?

STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You feel pain in your stomach	0	1	2	3	4
2. They give you stomach pains	0	1	2	3	4
3. Your stomach hurts	0	1	2	3	4
4. You wake up at night with stomach pain	0	1	2	3	4
5. Your stomach turns	0	1	2	3	4
6. You have an upset stomach	0	1	2	3	4

STOMACH DISCOMFORT WHEN EATING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. When you eat, your stomach turns	0	1	2	3	4
2. When you eat, you feel sick to your stomach	0	1	2	3	4
3. Your stomach hurts when you eat	0	1	2	3	4
4. You feel a heavy stomach when you eat	0	1	2	3	4
5. As soon as you start eating, you feel full.	0	1	2	3	4

FOOD AND DRINK LIMITS (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You can't eat some foods	0	1	2	3	4
2. You can't drink some drinks	0	1	2	3	4
3. You can't eat what you want	0	1	2	3	4
4. You can't drink what you want	0	1	2	3	4
5. You can't eat some foods because they upset your stomach.	0	1	2	3	4
6. He can't eat the foods his friends eat	0	1	2	3	4

DIFFICULTY SWALLOWING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You find it difficult to swallow food	0	1	2	3	4
2. It hurts when you swallow	0	1	2	3	4
3. Food gets stuck as it passes by	0	1	2	3	4

ACIDITY AND REFLUX (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You feel a burning sensation in your throat	0	1	2	3	4

2. You feel pain in your stomach	0	1	2	3	4
3. Food returns to your mouth after eating	0	1	2	3	4

NAUSEA AND VOMITING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You feel like vomiting	0	1	2	3	4
2. You feel like vomiting when you eat	0	1	2	3	4
3. You feel like vomiting after eating	0	1	2	3	4
4. Vomit	0	1	2	3	4

GASES AND SWELLING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. Your stomach feels full of gas (farts)	0	1	2	3	4
2. Your stomach feels very full	0	1	2	3	4
3. Your stomach swells and becomes hard	0	1	2	3	4
4. It has a lot of gases	0	1	2	3	4
5. Expels a lot of gases	0	1	2	3	4
6. You feel like you have gas in your stomach	0	1	2	3	4
7. Your stomach makes noises	0	1	2	3	4

CONSTIPATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You still feel full after having pooped	0	1	2	3	4
2. You feel like you're not done after you've pooped.	0	1	2	3	4
3. You feel like you can't get your stool to come out completely.	0	1	2	3	4
4. It's painful when you poop	0	1	2	3	4
5. Your stools are hard	0	1	2	3	4
6. Your stool is lumpy or chunky	0	1	2	3	4
7. You have to use a lot of force to be able to poop.	0	1	2	3	4
8. Poop gets stuck when you have a bowel movement	0	1	2	3	4
9. Your butt hurts after you poop.	0	1	2	3	4
10. Poop takes a long time to come out	0	1	2	3	4
11. He has to work hard to get the poop out.	0	1	2	3	4
12. He doesn't want to poop because it hurts.	0	1	2	3	4

13. Spends a lot of time on the toilet pooping	0	1	2	3	4
14. Your stomach hurts when you poop.	0	1	2	3	4

BLOOD IN Stool (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. There is blood on the toilet paper after he poops.	0	1	2	3	4
2. There is blood in your stool	0	1	2	3	4

DIARRHEA (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You need to be near a bathroom very often	0	1	2	3	4
2. He has to run to the bathroom to poop	0	1	2	3	4
3. You feel like you're always in the bathroom pooping.	0	1	2	3	4
4. He wakes up at night to poop	0	1	2	3	4
5. The stools are watery	0	1	2	3	4
6. He poops in his underwear accidentally.	0	1	2	3	4
7. You have to evacuate many times	0	1	2	3	4

CONCERN ABOUT POOPING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. He worries about pooping his pants.	0	1	2	3	4
2. You are worried about not making it to the bathroom on time.	0	1	2	3	4
3. You worry about hurting yourself when you poop.	0	1	2	3	4
4. You are worried about having to use the bathroom at school	0	1	2	3	4
5. He worries about pooping his pants at school.	0	1	2	3	4

CONCERN ABOUT STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. You are worried about your stomach pain	0	1	2	3	4
2. You are worried about getting a stomachache at school.	0	1	2	3	4

MEDICINES (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for him/her to take his/her	0	1	2	3	4

medications					
2. You forget to take your medicines	0	1	2	3	4
3. It is hard for him/her to swallow his/her medicines	0	1	2	3	4
4. He doesn't like having to take his medicine all the time.	0	1	2	3	4

COMMUNICATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for him/her to tell doctors and nurses how he/she feels	0	1	2	3	4
2. It is hard for him/her to ask doctors and nurses some questions	0	1	2	3	4
3. It is hard for him/her to explain his/her illness to other people.	0	1	2	3	4
4. It is hard for him/her to explain his/her illness to his/her friends.	0	1	2	3	4
5. It is hard for him/her to talk about his/her illness with his/her parents.	0	1	2	3	4

Annex 6. PedsQL 3.0 - Gastrointestinal Symptoms Module. Children's report

Name:_____

Date:_____ / _____ / _____

PedsQLTM

Gastrointestinal Symptoms Module

Version 3.0

CHILDREN REPORT (ages 8-12)

INSTRUCTIONS

On the next page is a list of things that could be a problem for you.

Please tell us, by circling or crossing out each answer, depending on how much trouble each thing has caused you in the last month:

0If it's never a problem

1Yes it is almost never a problem

2Yes sometimes it is a problem

3Yes it is often a problem

4Yes it is almost always a problem

There are not correct or incorrect answers.

If you do not understand any question, please ask for help.

In the last month, how much of a problem has this been for you…?

STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I feel pain in my stomach	0	1	2	3	4
2. I feel sore in my stomach	0	1	2	3	4
3. My stomach hurts	0	1	2	3	4
4. I wake up at night with a stomach ache	0	1	2	3	4
5. My stomach turns	0	1	2	3	4
6. I have an upset stomach	0	1	2	3	4

STOMACH DISCOMFORT WHEN EATING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. When I eat, my stomach turns	0	1	2	3	4
2. When I eat, I feel sick to my stomach	0	1	2	3	4
3. My stomach hurts when I eat	0	1	2	3	4
4. I feel heaviness in my stomach when I eat	0	1	2	3	4
5. As soon as I start eating, I feel full.	0	1	2	3	4

FOOD AND DRINK LIMITS (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I can't eat some foods	0	1	2	3	4
2. I can't have some drinks	0	1	2	3	4
3. I can't eat what I want	0	1	2	3	4
4. I can't drink what I want	0	1	2	3	4
5. I can't eat some foods because they upset my stomach.	0	1	2	3	4
6. I can't eat the foods my friends eat	0	1	2	3	4

DIFFICULTY SWALLOWING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I find it difficult to swallow food	0	1	2	3	4
2. It hurts when I swallow	0	1	2	3	4
3. Food gets stuck when it passes by	0	1	2	3	4

ACIDITY AND REFLUX (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always

1. I feel burning in my throat	0	1	2	3	4
2. I have chest pain or discomfort	0	1	2	3	4
3. My food returns after eating	0	1	2	3	4

NAUSEA AND VOMITING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I feel like vomiting	0	1	2	3	4
2. I feel like vomiting when I eat	0	1	2	3	4
3. I feel like vomiting after eating	0	1	2	3	4
4. Vomiting	0	1	2	3	4

GASES AND SWELLING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. My stomach feels full of gas	0	1	2	3	4
2. My stomach feels very full	0	1	2	3	4
3. My stomach swells and becomes hard	0	1	2	3	4
4. I have a lot of gas (belching)	0	1	2	3	4
5. I expel a lot of gas (farts)	0	1	2	3	4
6. I feel like I have gas in my stomach	0	1	2	3	4
7. My stomach makes noises	0	1	2	3	4

CONSTIPATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I still feel full after pooping	0	1	2	3	4
2. I feel like I'm not done after pooping.	0	1	2	3	4
3. I feel like I can't get the poop to come out completely.	0	1	2	3	4
4. It hurts when I poop	0	1	2	3	4
5. My stools are hard	0	1	2	3	4
6. My stool is lumpy	0	1	2	3	4
7. I have to use a lot of force to poop.	0	1	2	3	4
8. My poop gets stuck	0	1	2	3	4
9. My butt hurts after pooping.	0	1	2	3	4
10. It takes a long time for the poop to come out	0	1	2	3	4
11. I have to try really hard to poop.	0	1	2	3	4
12. I don't want to poop because it hurts.	0	1	2	3	4
13. I spend a lot of time on the toilet pooping.	0	1	2	3	4

14. My stomach hurts when I poop.	0	1	2	3	4

BLOOD IN Stool (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. There is blood on the toilet paper after I poop.	0	1	2	3	4
2. There is blood in my poop	0	1	2	3	4

DIARRHEA (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I need to be near a bathroom very often	0	1	2	3	4
2. I have to run to the bathroom to poop.	0	1	2	3	4
3. I feel like I'm always in the bathroom pooping.	0	1	2	3	4
4. I wake up at night to poop.	0	1	2	3	4
5. My stools are watery	0	1	2	3	4
6. I accidentally poop in my underwear.	0	1	2	3	4
7. I have to poop a lot	0	1	2	3	4

CONCERN ABOUT POOPING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I worry about pooping my pants.	0	1	2	3	4
2. I worry about not getting to the bathroom on time.	0	1	2	3	4
3. I worry about hurting myself when I poop.	0	1	2	3	4
4. I worry about having to use the bathroom at school	0	1	2	3	4
5. I worry about pooping my pants at school.	0	1	2	3	4

CONCERN ABOUT STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I am worried about my stomach pain	0	1	2	3	4
2. I worry that my stomach will hurt at school.	0	1	2	3	4

MEDICINES (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for me to take my medicines	0	1	2	3	4
2. I forget to take my medicines	0	1	2	3	4
3. It is hard for me to swallow my medicines	0	1	2	3	4
4. I don't like having to take my medicine all the	0	1	2	3	4

time.					

COMMUNICATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for me to tell doctors and nurses how I feel.	0	1	2	3	4
2. It is hard for me to ask doctors and nurses some things.	0	1	2	3	4
3. It is hard to explain my illness to other people	0	1	2	3	4
4. It is hard to explain my illness to my friends	0	1	2	3	4
5. It is hard to talk about my illness with my parents	0	1	2	3	4

Annex 7. PedsQL 3.0 - Gastrointestinal Symptoms Module. Teen Report

Name:_____

Date:_____ / _____ / _____

PedsQLTM

Gastrointestinal Symptoms Module

Version 3.0

TEEN REPORT (ages 13-18)

INSTRUCTIONS

On the next page is a list of things that could be a problem for you.

Please tell us, by circling or crossing out each answer, depending on how much trouble each thing has caused you in the last month:

0If it's never a problem

1Yes it is almost never a problem

2Yes sometimes it is a problem

3Yes it is often a problem

4Yes it is almost always a problem

There are not correct or incorrect answers.

If you do not understand any question, please ask for help.

In the last month, how much of a problem has this been for you…?

STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I feel pain in my stomach	0	1	2	3	4
2. I feel sore in my stomach	0	1	2	3	4
3. My stomach hurts	0	1	2	3	4
4. I wake up at night with a stomach ache	0	1	2	3	4
5. My stomach turns	0	1	2	3	4
6. I have an upset stomach	0	1	2	3	4

STOMACH DISCOMFORT WHEN EATING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. When I eat, my stomach turns	0	1	2	3	4
2. When I eat, I feel sick to my stomach	0	1	2	3	4
3. My stomach hurts when I eat	0	1	2	3	4
4. I feel heaviness in my stomach when I eat	0	1	2	3	4
5. As soon as I start eating, I feel full.	0	1	2	3	4

FOOD AND DRINK LIMITS (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I can't eat some foods	0	1	2	3	4
2. I can't have some drinks	0	1	2	3	4
3. I can't eat what I want	0	1	2	3	4
4. I can't drink what I want	0	1	2	3	4
5. I can't eat some foods because they upset my stomach.	0	1	2	3	4
6. I can't eat the foods my friends eat	0	1	2	3	4

DIFFICULTY SWALLOWING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I find it difficult to swallow food	0	1	2	3	4
2. It hurts when I swallow	0	1	2	3	4
3. Food gets stuck when it passes by	0	1	2	3	4

ACIDITY AND REFLUX (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I feel burning in my throat	0	1	2	3	4

2. I have chest pain or discomfort	0	1	2	3	4
3. My food returns after eating	0	1	2	3	4

NAUSEA AND VOMITING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I feel like vomiting	0	1	2	3	4
2. I feel like vomiting when I eat	0	1	2	3	4
3. I feel like vomiting after eating	0	1	2	3	4
4. Vomiting	0	1	2	3	4

GASES AND SWELLING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. My stomach feels full of gas	0	1	2	3	4
2. My stomach feels very full	0	1	2	3	4
3. My stomach swells and becomes hard	0	1	2	3	4
4. I have a lot of gas (belching)	0	1	2	3	4
5. I expel a lot of gas (farts)	0	1	2	3	4
6. I feel like I have gas in my stomach	0	1	2	3	4
7. My stomach makes noises	0	1	2	3	4

CONSTIPATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I still feel full after pooping	0	1	2	3	4
2. I feel like I'm not done after pooping.	0	1	2	3	4
3. I feel like I can't get the poop to come out completely.	0	1	2	3	4
4. It hurts when I poop	0	1	2	3	4
5. My stools are hard	0	1	2	3	4
6. My stool is lumpy	0	1	2	3	4
7. I have to use a lot of force to poop.	0	1	2	3	4
8. My poop gets stuck	0	1	2	3	4
9. My butt hurts after pooping.	0	1	2	3	4
10. It takes a long time for the poop to come out	0	1	2	3	4
11. I have to try really hard to poop.	0	1	2	3	4
12. I don't want to poop because it hurts.	0	1	2	3	4
13. I spend a lot of time on the toilet pooping.	0	1	2	3	4
14. My stomach hurts when I poop.	0	1	2	3	4

BLOOD IN Stool (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. There is blood on the toilet paper after I poop.	0	1	2	3	4
2. There is blood in my poop	0	1	2	3	4

DIARRHEA (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I need to be near a bathroom very often	0	1	2	3	4
2. I have to run to the bathroom to poop.	0	1	2	3	4
3. I feel like I'm always in the bathroom pooping.	0	1	2	3	4
4. I wake up at night to poop.	0	1	2	3	4
5. My stools are watery	0	1	2	3	4
6. I accidentally poop in my underwear.	0	1	2	3	4
7. I have to poop a lot	0	1	2	3	4

CONCERN ABOUT POOPING (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I worry about pooping my pants.	0	1	2	3	4
2. I worry about not getting to the bathroom on time.	0	1	2	3	4
3. I worry about hurting myself when I poop.	0	1	2	3	4
4. I worry about having to use the bathroom at school	0	1	2	3	4
5. I worry about pooping my pants at school.	0	1	2	3	4

CONCERN ABOUT STOMACH PAIN (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. I am worried about my stomach pain	0	1	2	3	4
2. I worry that my stomach will hurt at school.	0	1	2	3	4

MEDICINES (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for me to take my medicines	0	1	2	3	4
2. I forget to take my medicines	0	1	2	3	4
3. It is hard for me to swallow my medicines	0	1	2	3	4
4. I don't like having to take my medicine all the time.	0	1	2	3	4

COMMUNICATION (problems with...)	Never	Hardly ever	Sometimes	Often	Almost always
1. It is hard for me to tell doctors and nurses how I feel.	0	1	2	3	4
2. It is hard for me to ask doctors and nurses some things.	0	1	2	3	4
3. It is hard to explain my illness to other people	0	1	2	3	4
4. It is hard to explain my illness to my friends	0	1	2	3	4
5. It is hard to talk about my illness with my parents	0	1	2	3	4

Annex 8. Weekly medication report (4 to 10 years)

- **It is important to take medications as directed by your doctor.**
- Make sure your child (patient) does not miss any doses.
- Inform your doctor immediately if you experience any side effects caused by taking a medication.
- Make sure the doctor is aware of any additional supplements, vitamins, or over-the-counter medications the patient takes.

Name:

Container: **#** **Start date:** **//** **End date:** **//**

Mark with a check mark (✔) the days on which you took the medication.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Indicate with a check mark (✔) if in the last 7 days you had any of the following reactions within the next 2 hours of taking the medication.

Dry mouth		Indigestion		Constipation	
Diarrhea		Nausea		Urticaria	
Headache		Dream		Fatigue	
Dizziness		Shaking chills		Bad breath	

Others: _____

Container: **#** **Start date:** **//** **End date:** **//**

Mark with a check mark (✔) the days on which you took the medication.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

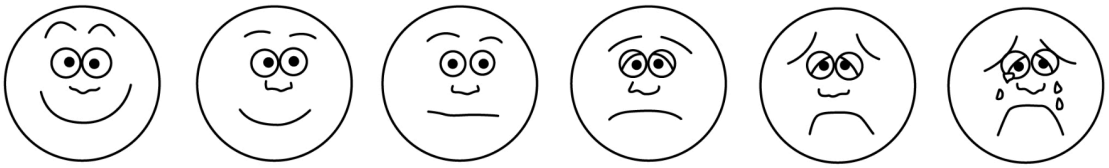
Indicate with a check mark (✔) if in the last 7 days you had any of the following reactions within the next 2 hours of taking the medication.

Dry mouth		Indigestion		Constipation			
Diarrhea		Nausea		Urticaria			
Headache		Dream		Fatigue			
Dizziness		Shaking chills		Bad breath			

Others: _____

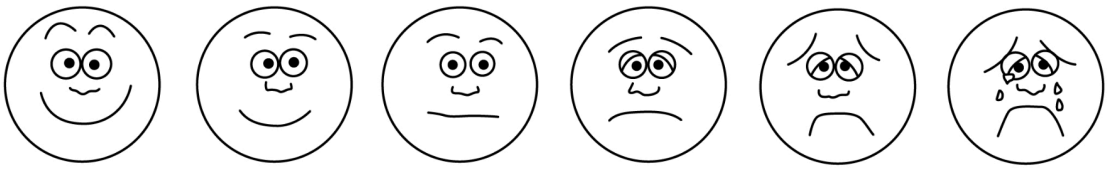
Wong-Baker FACES® Pain Scale.

Choose the face that best describes how your child feels now.



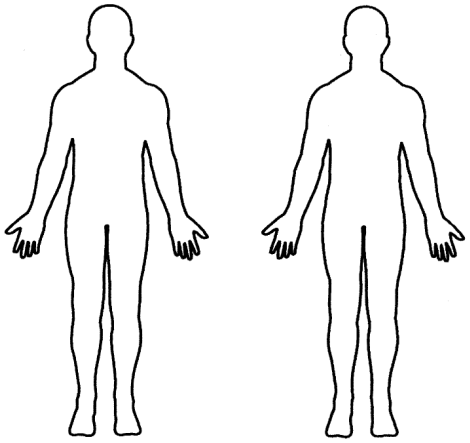
0	2	4	6	8	10
It does not hurt	It hurts a little	It hurts a little more	It hurts even more	It hurts much	The worst pain

Choose the face that best describes the worst pain your child had during the last 7 days.



0	2	4	6	8	10
It does not hurt	It hurts a little	It hurts a little more	It hurts even more	It hurts much	The worst pain

Mark with an X the exact place where you have pain now. If you have pain in more than one place, mark '1', '2', '3', etc., starting with '1' for the most painful place.



Annex 9. Weekly medication report (10 to 18 years old)

- **It is important to take medications as directed by your doctor.**
- Make sure your child (patient) does not miss any doses.
- Inform your doctor immediately if you experience any side effects caused by taking a medication.
- Make sure the doctor is aware of any additional supplements, vitamins, or over-the-counter medications the patient takes.

Name:

Container: **#** **Start date:** **//** **End date:** **//**

Mark with a check mark (✔) the days on which you took the medication.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Indicate with a check mark (✔) if in the last 7 days you had any of the following reactions within the next 2 hours of taking the medication.

Dry mouth		Indigestion		Constipation	
Diarrhea		Nausea		Urticaria	
Headache		Dream		Fatigue	
Dizziness		Shaking chills		Bad breath	

Others: _____

Container: **#** **Start date:** **//** **End date:** **//**

Mark with a check mark (✔) the days on which you took the medication.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

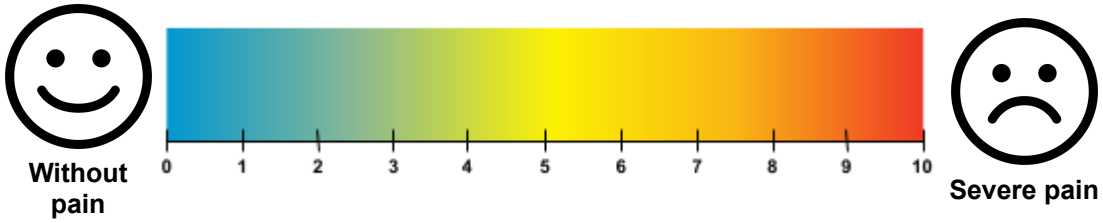
Indicate with a check mark (✔) if in the last 7 days you had any of the following reactions within the next 2 hours of taking the medication.

Dry mouth		Indigestion		Constipation	
Diarrhea		Nausea		Urticaria	
Headache		Dream		Fatigue	
Dizziness		Shaking chills		Bad breath	

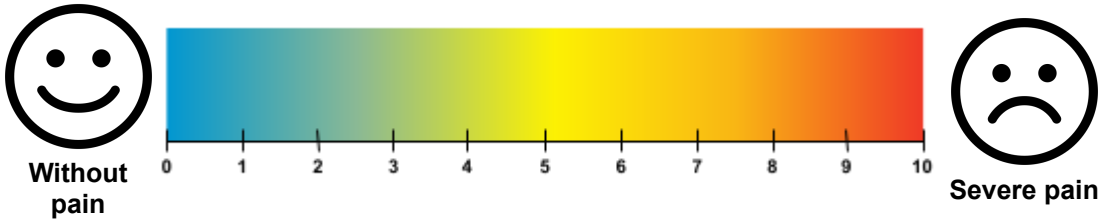
Others: _____

Visual Analogue Scale (VAS) of Pain.

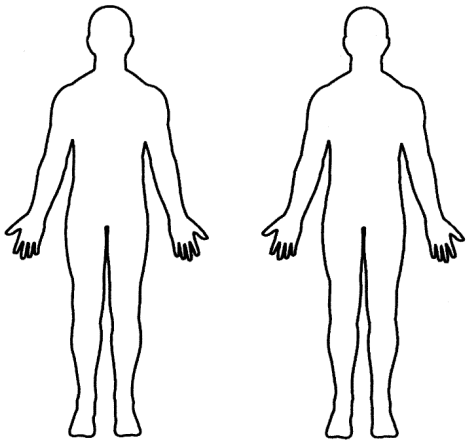
Put a check on the line to show how you feel now.



Put a mark on the line to show the worst pain you had during the last 7 days.



Mark with an X the exact place where you have pain now. If you have pain in more than one place, mark '1', '2', '3', etc., starting with '1' for the most painful place.



Annex 10. Letter of no conflict of interest

Colima, Col., October 25, 2023

Dr. Gabriel Ramirez Patiño

Director of the Hospital Regional Universitario de Colima

No conflict of interest letter

Hereby, I, C. Pablo Hernan Sandoval Villaseñor, Principal Investigator, student of the Master's Degree in Medical Sciences at the School of Medicine of the Universidad de Colima, and the thesis advisors Mr. C. Fabián Rojas Larios, Medical Specialist A, assigned to the Teaching, Training and Research Unit, and Dr. C. Carmen Alicia Sánchez Ramírez, Medical Specialist in Pediatrics, External Associate Researcher, we declare that we have no conflict of interest in relation to the research protocol titled "EFFECT OF TRIMEBUTINE VS PROBIOTICS ON FUNCTIONAL ABDOMINAL PAIN IN CHILDREN: RANDOMIZED CLINICAL TRIAL."

We confirm that we do not have any financial, personal or professional relationships with other people or organizations that could inappropriately influence our work. We have not received any funding to carry out this study, which was carried out with our own funds.

We undertake to inform the Research Committee (IC) and the Ethics and Research Committee (CEI) of any change in the study protocol or in the situation of the researchers that may give rise to a conflict of interest. We appreciate your attention and remain at your disposal for any additional information you may require.

Sincerely,

C. Pablo Hernan Sandoval Villaseñor	**D. in C. Fabián Rojas Larios**	**D. in C. Carmen Alicia Sánchez Ramírez**
Principal investigator	Methodological advisor	Clinical advisor

Annex 11. Checklist (CONSORT reporting guidelines) for randomized clinical trials(40).

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 (https://www.goodreports.org/reporting-checklists/consort/).

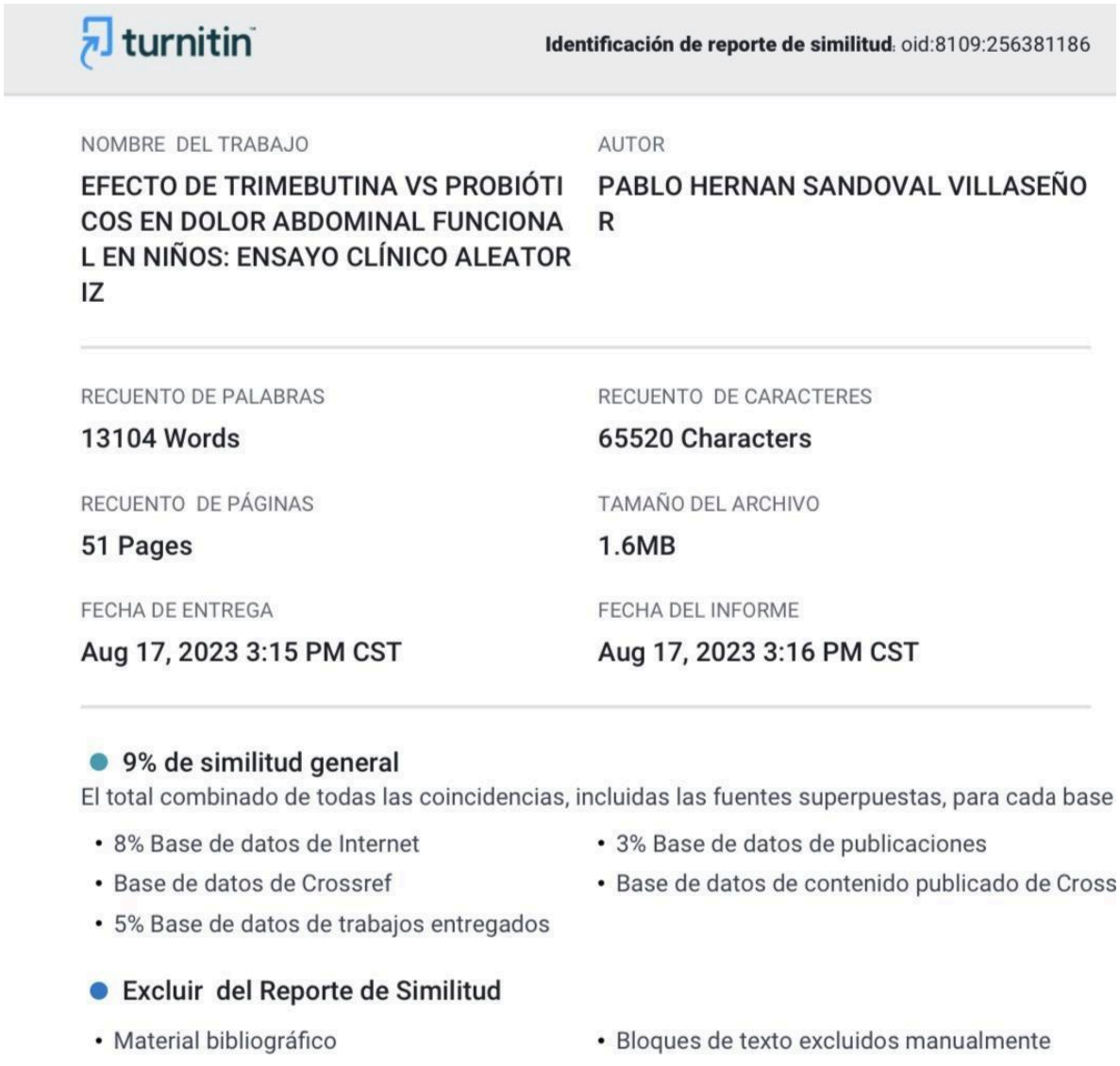
Section	Item number	☑	P
Title and summary			
1a. Qualification	It is identified as a randomized clinical trial in the title.	●	1
1 B. Summary	Structured summary of the trial design, methods, results and conclusions.	●	SUMMARY:PEND
Introduction			
2a. Background	Scientific background and explanation of the fundamentals.	●	THEORETICAL FRAMEWORK
2b. Goals	Specific objectives or hypotheses.	●	Goals
Methods			
3a. Trial design	Description of trial design (such as parallel, factorial), including allocation rate.	●	Study design
3b. Trial design	Major changes in methods after the start of the trial (such as eligibility criteria), with reasons.	●	N/A
4a. Participants	Eligibility criteria for participants.	●	Selection criteria
4b. Participants	Environments and locations where data was collected.	●	Study universe
5. Interventions	Experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered.	●	Variables
6a. Results	Fully defined pre-specified primary and secondary outcome measures, including how and when they were assessed.	●	PEND
6b. Results	Any change in the results of the trial after its start, with its reasons.	●	N/A
7a. Sample size	How the sample size was determined.	●	Sample size
7b. Sample size	Where applicable, explanation of any interim analysis and stopping guidelines.	●	N/A

Section	Item number	☑	P
8a. Randomization: generation.	Method used to generate the random assignment sequence.	●	Sampling method
8b. Randomization: generation.	Type of randomization; details of any restrictions (such as blocking and block size).	●	Sampling method
9. Randomization: allocation hiding mechanism	Mechanism used to implement the randomization sequence (such as sequentially numbered bins), describing any steps taken to conceal the sequence until interventions were assigned.	●	Methodological description
10. Randomization implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to the interventions.	●	Methodological description
11a. Masking	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how.	●	Methodological description
11b. Masking	If applicable, description of the similarity of the interventions.	●	N/A
12a. Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes.	●	Statistical analysis and data interpretation
12a. Statistical methods	Methods for additional analyses, such as subgroup analyzes and adjusted analyses.	●	Statistical analysis and data interpretation
Results			
13a. Participant flowchart	For each group, the number of participants who were randomized, received the intended treatment, and were analyzed for the primary outcome.	●	Methodological description
13b. Participant flowchart	For each group, losses and exclusions after randomization, along with the reason.	●	Methodological description
14 to. Recruitment	Dates that define the contracting and monitoring periods.	●	SCHEDULE OF ACTIVITIES
14b. Recruitment	Why the trial ended or was stopped.	●	N/A
15. Reference data	A table showing the baseline demographic and clinical characteristics of each group.	●	PEND.
16. Participants analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was performed by originally assigned groups.	●	PEND.
17a. Results and estimation	For each primary and secondary outcome, the results for each group and the estimated effect size and its precision (such as the 95% confidence interval).	●	PEND.

Section	Item number	☑	P
17b. Results and estimation	For binary results, presentation of absolute and relative effect sizes is recommended.	●	PEND.
18. Auxiliary analyzes	Results of any other analyzes performed, including subgroup analyzes and adjusted analyses, distinguishing prespecified from exploratory.	●	PEND.
19. Adverse effects	Any major damage or unwanted effects in each group (for specific guidance, see CONSORT for damage).	●	PEND.
Discussion			
20. Limitations	Limitations of the trials, addressing sources of possible bias, imprecision and, if relevant, multiplicity of analyses.	●	PEND.
21. Generability	Generalizability (external validity, applicability) of the trial findings.	●	PEND.
22. Interpretation	Interpretation consistent with the results, weighing benefits and harms, and considering other relevant evidence.	●	PEND.
Other information			
23. Registration	Registration number and name of the trial record.	●	PEND.
24. Protocol	Where the full trial protocol can be accessed, if available.	●	PEND.
25. Financing	Sources of financing and other types of support (such as the provision of medicines), role of funders.	●	FINANCING

* Adapted from Schulz, et al., 2010(40).

Annex 12. Turnitin Similarity Report



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AUTOR

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Annex 13. Bioethics Committee Approval of the School of Medicine

UNIVERSIDAD DE COLIMA
FACULTAD DE MEDICINA

COMITÉ DE BIOÉTICA

C. Investigador: **Fabián Rojas Larios**

PROYECTO: "EFECTO DE TRIMEBUTINA VS PROBIÓTICOS EN DOLOR ABDOMINAL FUNCIONAL EN NIÑOS: ENSAYO CLÍNICO ALEATORIZADO".

Reg. **2023-5**

En atención a su solicitud del día 8 de noviembre de 2023 para que el proyecto arriba mencionado, bajo su dirección, se sometiera a revisión por parte del Comité de Ética en Investigación de la Facultad de Medicina, se le comunica que dicho proyecto ha sido

APROBADO CON CORRECCIONES MÍNIMAS

En base al reglamento vigente para esta comisión y en concordancia con la Ley General de Salud en materia de Investigación.

Se extiende la presente a los 9 días del mes de enero de 2024, para los trámites a que haya lugar.