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Effect of faecal calprotectin testing on referrals for children with chronic gastrointestinal symptoms in primary care: study protocol for a cluster randomised controlled trial

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Effect of faecal calprotectin testing on referrals for children with chronic gastrointestinal symptoms in primary care: study protocol for a cluster randomised controlled trial

S.M. Ansems[1], G.A. Holtman[1], P.F. van Rheenen[2], K.M. Vermeulen[3], G.G. Beugel[1], M.P.E. Couwenberg[1], M.Y. Berger[1]

1. Department of General Practice, University Medical Center Groningen, University of Groningen, the Netherlands
2. Department of Paediatric Gastroenterology, University Medical Center Groningen, University of Groningen, the Netherlands
3. Department of Epidemiology, University Medical Center Groningen, University of Groningen, the Netherlands

Corresponding author: Sophie M. Ansems | Department of General Practice and Elderly Care Medicine, FA21, University of Groningen, University Medical Centre Groningen, PO Box 196, 9700 AD Groningen, The Netherlands | E-mail: s.m.ansems@umcg.nl | +31 6 14186134

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ABSTRACT

Introduction: Children with chronic gastrointestinal symptoms are frequently seen in primary care, yet general practitioners (GPs) often experience challenges distinguishing functional gastrointestinal disorders (FGID) from somatic disorders. We therefore aim to evaluate whether a test strategy that includes point-of-care testing (POCT) for faecal calprotectin (FCal) can reduce the referral rate to paediatric specialist care among children with chronic gastrointestinal symptoms. The study findings will contribute to improving the recommendations on FCal use among children in primary care.

Methods and analysis: In this pragmatic cluster randomised controlled trial, we will randomise general practices into intervention and control groups. The intervention group will use FCal-POCT when indicated, after completing online training about its indication, interpretation, and follow-up, as well as communicating an FGID diagnosis. The control group will test and treat according to Dutch GP guidelines, which advise against FCal testing in children. GPs will include children aged 4–18 years presenting to primary care with chronic diarrhoea or recurrent abdominal pain. The primary outcome will be the referral rate for children with chronic gastrointestinal symptoms within 6 months after the initial assessment. Secondary outcomes will be evaluated by questionnaires completed at baseline and at 3- and 6-months' follow-up. These outcomes will include parental satisfaction and concerns, gastrointestinal symptoms, impact of symptoms on daily function, quality of life, proportion of children with paediatrician-diagnosed FGID referred to secondary care, health service use and health care costs. A sample size calculation indicates that we need to recruit 158 GP practices to recruit 406 children.

Ethics and Dissemination: The Medical Research Ethics Committee (MREC) of the University Medical Center Groningen (Netherlands) approved this study (MREC-number: 201900309). The study results will be made available to patients, GPs, paediatricians, and laboratories via peer-reviewed publications and in presentations at (inter)national conferences.

Registration details: The Netherlands Trial Register: NL7690

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Faecal calprotectin (FCal) has high diagnostic value in children in primary care, but it is not known if its use delivers sufficient benefits to patients or if its cost justifies routine use.
- To facilitate optimal FCal use, we believe that training about the indication, interpretation, follow-up and communication of FCal results will be key to introducing this point-of-care test.
- The study results can be directly translated to daily practice in primary care because of its pragmatic design and the incorporation of the test strategy in routine clinical practice.
- Due to this pragmatic design, GPs will not be blinded to either group allocation or study outcomes.
- The cluster design means that we must be aware of the risk of selection bias.

ABBREVATIONS

CONSORT	Consolidated Standards of Reporting Trials
EQ-5D-Y	EuroQol Youth
FCal	Faecal Calprotectin
FDI	Functional Disability Inventory
FGID	Functional gastrointestinal disorders
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
IBD	Inflammatory bowel disease
ICPC	International Classification of Primary Care
MREC	Medical Research Ethics Committee
POCT	Point-of-care testing
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

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INTRODUCTION

Background and rationale

A Dutch general practitioner (GP) typically sees approximately 10 children with chronic gastrointestinal symptoms each year (1,2). At least 90% of these children will have functional gastrointestinal disorders (FGID) (3), but before this diagnosis can be made, inflammatory bowel disease (IBD), celiac disease, and other causes must be excluded. However, it is a diagnostic challenge to differentiate between FGID and these organic diseases because their clinical presentations can be very similar. Referring and testing children to identify these low prevalent disorders then delays appropriate treatment for FGID and can lead to unnecessary suffering (4,5). Additionally, we want to prevent specialists' time taken up with FGID, as it is considered a complex and time-consuming problem in specialist care (1). At the same time, it is critical that we avoid delaying the diagnosis and treatment of IBD and celiac disease to minimise complications such as anaemia and growth failure, and in the case of IBD, delayed sexual maturation (6,7).

The Dutch Society of General Practitioners (*Nederlands Huisartsen Genootschap*; NHG) recommends additional testing for suspected celiac disease and blood tests for suspected IBD (e.g., haemoglobin, leukocytes and ESR) (8). However, these blood tests cannot exclude IBD, having a sensitivity of only 0.43–0.57 (9–11), and they suffer from being invasive and potentially traumatic for children (12). By contrast, faecal calprotectin (FCal) is a non-invasive marker of intestinal inflammation that has been shown in recent observational studies to exclude IBD safely in children with chronic gastrointestinal symptoms and additional alarm symptoms in primary care settings (sensitivity, 0.99–1.00; 95% CI, 0.81–1.00)(13–15). When tested in children without alarm symptoms, however, the positive predictive value decreases due to the low prevalence (<1%) of IBD in this population (16). The number of children referred for further diagnostic evaluation may therefore increase unintentionally.

The last decade has seen an increasing focus on point-of-care-testing (POCT) in primary care to improve rapid decision making and triage at the time and place of patient care (17–19). FCal is

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available as a POCT for which results are available the same day and samples do not need to be sent to a laboratory, yet it retains characteristics that are comparable to the standard laboratory test (20–22). Therefore, the FCal-POCT could decrease a GPs diagnostic uncertainty and provide early reassurance for both parents and children that a potential harmful disease (IBD) can be safely excluded. To optimise FCal-POCT implementation, proper training is needed about its indication, interpretation, and follow-up (17). Perceived parental pressure for a referral is another relevant factor that may influence the decision to refer children with chronic gastrointestinal symptoms. Therefore, GPs must also receive communication skills training to explain the results, the pros and cons of referral, the natural course of (functional) symptoms and when to consult again (23).

Hypothesis

We hypothesise that FCal-POCT, when combined with online training about the indication, interpretation, follow-up of testing and communicating an FGID diagnosis, will increase patient satisfaction and substantially reduce the referral rate for children with chronic gastrointestinal symptoms from primary to secondary care, as compared to usual care.

METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (24) and the extended Consolidated Standards of Reporting Trials (CONSORT) statement for cluster trials (25).

Design and setting

This is a pragmatic clustered randomised controlled trial with 1:1 randomisation, at the level of the GP practice, to either an intervention group or a control group (see Figure 1). From October 2019 to October 2020, GP practices in the Netherlands will be invited to participate in the study. The Netherlands has a primary health care system in which the GP functions as the gatekeeper to specialist (i.e., paediatric) care, comparable to the systems in among others Canada and the United Kingdom. Participating GPs will include children between October 2019 and October 2021.

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The primary outcome (referral to paediatric specialist care) will be assessed at an individual level within 6 months after baseline GP consultation, defined as the first consultation at which a child meets the criteria for inclusion.

Study population

Every general practice in the Netherlands is eligible for participation in our study, including all GPs and GP trainees working at those practices. GPs will be asked to include children meeting the following criteria: age 4–18 years; with chronic diarrhoea (defined as soft to watery stool for ≥2 weeks or ≥2 episodes in the past 2 months); and/or with recurrent or chronic abdominal pain (defined as abdominal pain with a recurrent character for ≥2 months or ≥2 episodes in the past 2 months). Children will be excluded if they have a history of chronic organic gastrointestinal disease (e.g. celiac disease or IBD) or if they have had an endoscopic evaluation, referral to paediatric care for gastrointestinal symptoms or an FCal result within the preceding 6 months.

Intervention and control group

Randomisation and blinding

GP practices will be randomised by a computer-generated list using varying block randomisation in 1:1 ratio by an independent researcher not involved in the project. To reduce the risk of contamination, all GPs working at a given GP practice will be allocated as a cluster in the same study arm. GPs, children, and parents will not be blinded to the intervention, but the research team will be blinded to study group assignment for the statistical analysis.

Control group: care as usual

GPs in the control group will provide care as usual according to the guidelines of the Dutch society for GPs, which recommends not using FCal testing in children (8,26–28). It will nevertheless still be possible for them to request laboratory FCal testing or to refer the child for further diagnostic testing, if deemed necessary. All GPs will receive an information leaflet about what is considered care as usual (Supplementary File 1).

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Intervention group: FCal-POCT plus online training

FCal-POCT devices will be made available to GPs for use in their practices, and each GP will be free to decide whether to use the FCal-POCT during baseline or follow-up consultation(s). All participating GPs will complete the obligatory online training and will receive the same information leaflet as the control group. However, this leaflet will be amended to recommend FCal instead of blood tests when IBD is suspected.

The FCal-POCT: IBDoc

The IB*Doc* home testing application (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) will be used. This is an *in vitro* diagnostic immunoassay for quantitatively determining faecal calprotectin in human stool (29). Originally developed for self-testing by trained patients at home, it is also suitable for use in near-patient or laboratory settings (29). In a recent head-to-head comparison of three FCal-POCT devices in children with IBD, the IB*Doc* device had the best agreement with ELISA and produced significantly fewer reading errors compared with the other FCal-POCT devices (22). In the intervention group, trained research staff will teach GP assistants to use the IB*Doc* device during a 60-minute face-to-face training session.

Online training for GPs

The content of the training was developed during two expert panel sessions with two academic paediatric gastroenterologists (PFR), two GPs (MYB and MPEC), a psychologist, an educationalist, a clinical epidemiologist (GAH) and a clinical chemist. In the first session, we formulated the FCal-POCT test strategy based on a review of the scientific literature (1,3,9,13,14,22). In the second session, the concept of the online training was adjusted according to the four domains of Kirkpatrick's model: reaction, learning, behaviour and results (30). Subsequently, the research team developed the online training (including video recordings) in close collaboration with the expert panel. The online training was tested by five GPs (academic and non-academic) before implementation.

The final 60-minute online training for GPs reflects the FCal-POCT test strategy. It has been shown

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that an FCal value <50 µg/g can safely exclude IBD in children in primary care (sensitivity of 0.99–1.00 [95% CI 0.81–1.00]) (13,14). Additionally, an FCal value >250 µg/g has a specificity of 0.98 (95% CI 0.92–0.99) (13). However, an FCal value >50 µg/g also has a high false-positive rate (13%) when tested in a population of children both with and without alarm symptoms (13). Therefore, it is recommended to test only those children with alarm symptoms, to monitor those with an FCal value of 50–250 µg/g and to refer those with an FCal value >250 µg/g. In addition to the indication and interpretation of cut off values, the online training includes detail on the follow-up of test results between 50 and 250 µg/g, how to communicate the FCal result and how to educate about FGID (9,31).

Figure 2 shows the flow chart for the test strategy. This features prominently throughout the online training and is given to GPs as a desk reminder. The online training contains five modules in total: an introduction module, three modules each covering a different patient case or test scenario, and a module with a proficiency test (Supplementary File 2). The online training uses text blocks, tables, graphs, images, videos (GP consultations with a child and parent) and interactive questions.

Outcomes

Primary outcome

The primary outcome is the proportion of referrals to secondary care within 6 months after the baseline consultation. Research staff will extract this information from the medical files of GPs.

Secondary outcomes

Parental satisfaction about baseline consultation

The Parental Medical Interview Scale (P-MISS) measures parent satisfaction with the GP consultation (32). This questionnaire assesses physician communication with the parent and child, distress relief, and adherence intent on a five-point Likert scale ranging from 'strongly disagree' (score = 1) to 'strongly agree' (score = 5). The questionnaire showed good construct validity and internal consistency (α = 0.86) (32,33).

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Parental concern at baseline and at 3 and 6 months

At the baseline consultation and after 3 and 6 months, parents will answer the question 'How concerned do you feel about your child's gastrointestinal symptoms?' on a numeric version of a visual analogue scale (scored 1 to 10, with 1 defined as 'not concerned' and 10 defined as 'extremely concerned'). At the baseline consultation, parents will complete an additional questionnaire about their concerns. This will cover if and where parents sought advice before contacting their physician, what their current concerns are, and how the physician could provide reassurance to both the parent and child (34).

Self-reported gastrointestinal symptoms at baseline and at 3 and 6 months

Self-reported gastrointestinal symptoms will be evaluated using a ten-item questionnaire that we have previously used in a study of the diagnostic value of FCal for IBD in primary care (35). This questionnaire assesses the presence of alarm symptoms, as well as the duration and severity of abdominal pain and/or diarrhoea.

Impact of gastrointestinal symptoms on the child's daily function at baseline and at 3 and 6 months

The impact of symptoms on daily function will be evaluated with the Functional Disability Inventory (FDI) (36). This assesses self-reported difficulty in physical and psychosocial functioning due to physical health over the past 2 weeks. Responses to 15 items are scored on five-point scales that range from 'no trouble' (0) to 'impossible' (4). Items are averaged to give a composite score. Cronbach's alpha coefficient for the FDI is reported to be 0.90 (36).

Child's quality of life at baseline and at 3 and 6 months

Quality of life will be evaluated with the EuroQol Youth (EQ-5D-Y), a generic measure for quality of life. This instrument includes five domains (i.e. mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) with three levels of severity (i.e. no problems, some problems, and a lot of problems) (37). The questionnaire is feasible for use by children (38).

The proportion of children referred to paediatric care with FGID over 6 months

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The proportion of children diagnosed with FGID by the paediatrician will be recorded among those referred to paediatric care. This information will be extracted from the child's medical records based on letters sent by the paediatrician to the GP.

Health care use over 6 months

For all children, we will collect the following data from medical records: diagnostic tests, referrals to health care providers other than a paediatrician, medication prescriptions, GP consultation frequency and health care use at hospital (Supplementary File 3).

Costs over 6 months

Units of medical consumption will be extracted from medical records for all children (see health care use). In addition, cost questionnaires will be completed by parents at baseline and at 3- and 6-months' follow-up. These will measure additional health care use, out-of-pocket expenses and productivity losses (absence from work) based on adapted versions of the iMCQ and the iPCQ (39).

Recruitment

We will invite all GP practices connected to the Academic General Practitioner Development Network (AHON; *Academisch Huisarts Ontwikkel Netwerk*) via an informational letter. This network comprises 473 urban and rural GP practices in the four northern provinces of the Netherlands, and it seeks to facilitate collaboration in research, education, and innovation in general practice. We will also approach GP practices throughout the Netherlands with which our research staff are connected.

GPs will recruit consecutive eligible children during baseline consultations for one year (Figure 3). Additionally, research staff will retrospectively search for eligible children in GP registration databases using a search strategy based on International Classification of Primary Care (ICPC) codes (Supplementary File 4). Together with a short introduction about the study provided by the GP, all included children and/or parents will receive a patient information letter and will be asked to provide informed consent for completing questionnaires. Consequently, secondary outcomes assessed with questionnaires will only be evaluated in children who provide this consent.

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Data collection

For each eligible child, independent of inclusion during or after consultation, the GP will complete a trial inclusion form detailing the inclusion/exclusion criteria, gender, date of birth, presence of alarm symptoms and use of FCal-POCT (the latter only in the intervention group). The trial inclusion form is then sent to the researchers, and for all included children, data will be retrieved from their medical files for each consultation (including baseline) over a 6-month follow-up period (Supplementary File 3). Children and/or parents who provide informed consent will also complete digital questionnaires via RedCap after consultations at baseline, 3 months and 6 months. The estimated time to complete each questionnaire is 15–20 minutes, and if they are not completed, the child and/or parents will automatically receive reminders via e-mail after 7 and 14 days.

Sample size

Based on our earlier study on the diagnostic value of FCal in primary care (13), as well as the cross-sectional study on the management of children with abdominal pain in primary care (3), we expect referrals of children with chronic gastrointestinal symptoms to reduce from 17% to 7%. To detect this difference with a power of 80% and a significance level of 5%, an individually randomised study would need 326 children (163 per arm). Given a mean cluster size of 3 and an intraclass correlation coefficient of 0.06 (23,40), we would need 366 children (183 per arm). Then, allowing for a loss to follow-up of 10%, this increases to 406 children (203 per arm) from 134 general practices (67 per arm). We assume that 15% of the practices will not recruit any children; therefore, we aim to recruit 158 general practices (79 per arm).

Analysis

We will use descriptive statistics to summarise the data of GPs and children in the intervention and control groups, starting with their baseline characteristics. Analysis for both the primary and secondary outcomes will initially be done on an intention-to-treat basis, with children analysed within the GP group in which they are registered, irrespective of the care received. Analyses will

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then be repeated for both the primary and secondary outcomes on a per protocol basis: in the intervention group, we will only include children who receive the intended diagnostic strategy (per the indications explained in the online training); and in the control group, we will only include children who did not undergo FCal testing. We will analyse the primary outcome by multilevel logistic regression modelling to account for the practice. The effect of the intervention on secondary parameters will be assessed by multilevel logistic (dichotomous variables) or linear (continuous variables) regression modelling, as appropriate.

Economic evaluation

Alongside the RCT, we will perform a cost-effectiveness study with two aims. The primary aim will be to study the incremental costs of FCal-POCT compared to care as usual from a societal perspective. If the new test strategy reduces the number of referrals, this will be visible as a cost reduction in the economic evaluation. An incremental cost-utility ratio will then be calculated, based on the EQ-5D-Y for assessing utility. The secondary aim will be to estimate the cost-effectiveness of FCal-POCT. Two incremental cost-effectiveness ratios will be calculated, using parental concern and parental satisfaction as effect parameters. Costs will be measured from a societal perspective, such that productivity losses incurred by parents will also be included. Health care consumption will be valued according to Dutch standard guidelines for economic evaluations (41). Bootstrap re-sampling will be performed on the costs (primary analysis) and on the cost–effect pairs (cost-effectiveness and cost-utility) to produce confidence intervals. Finally, cost-effectiveness planes and acceptability curves will be plotted.

Patient and public involvement

We have collaborated with the Foundation Child and Hospital (*Stichting Kind en Ziekenhuis*) and have incorporated their opinions and expertise in the grant proposal, patient information letters and recruitment strategies. Moreover, we will ask them to help disseminate the study results to the public. In addition, we will distribute the study results to participating children and/or parents via a short e-mail newsletter. The Dutch Gastroenterology and Hepatology Foundation

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supports our research question and will also be involved in the dissemination of results.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The Medical Research Ethics Committee (MREC) of the University Medical Center Groningen (Netherlands) (MREC-number: 201900309) approved this study. The ethics committee waived the requirement to obtain written informed consent for collecting data from patients' medical files, according to Dutch law (Medical Treatment Contracts Act). This was allowed because asking for written informed consent from children and/or their parents could jeopardise recruitment. Additionally, it will reduce the risk of selection bias and increase the generalizability of our results to a real-world setting. For the assessment of secondary outcomes by questionnaires, informed consent will be obtained either from parents alone (child <12 years), parents and child (child 12–15 years) or the child alone (>15 years), consistent with Dutch law. Additionally, all participating GP practices will be required to sign a study agreement consenting to study protocol adherence and data collection by researchers from medical files. Important protocol changes will be communicated to the ethics committee and participating practices.

Dissemination

We aim to embed our study results in clinical practice. The findings will therefore be made available to patients, GPs, paediatricians, and laboratories via presentations at national and international conferences, social media, and peer-reviewed publications, irrespective of the magnitude or direction of effect. Within current national and international guidelines, there is a knowledge gap about the use of FCal in children in primary care. As such, our results will provide high quality evidence according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria because we include the impact on patient-important outcomes (42).

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DISCUSSION

To the best of our knowledge, this is the first trial designed to evaluate the effect of using FCal in the diagnostic process of GPs and how this affects referral rates for children with chronic gastrointestinal symptoms. We assume that children and/or parents in the intervention group will have improved patient-important outcomes due to the reduced diagnostic uncertainty. As such, we hypothesise that the referral rate will decrease. Although additional costs will be incurred by using FCal-POCT in the intervention group, we expect total costs to be lower compared to usual care because of the reduced use of other health care services (e.g. fewer GP consultations, blood tests and referrals), as well as less productivity loss for parents.

There is increasing awareness that new medical tests should have scientifically proven patient benefits before they are implemented in health care guidelines. In 2014, Horvath et al. described a new cyclical framework for evaluating in vitro medical tests, and this consisted of analytical and clinical performance, clinical and cost-effectiveness, and broader impact (43). The first step in Horvath's framework, analytical and clinical performance, has already been evaluated for FCal-POCT (13,20). In this trial, we will evaluate the impact of the test in daily practice, focusing on its clinical effectiveness and cost-effectiveness. An additional qualitative study is also needed to evaluate the broader impact of the FCal-POCT in primary care among GPs, GP assistants, parents, and children. If our hypothesis is confirmed, we anticipate that there may be sufficient evidence to include a recommendation on the use of FCal-POCT in relevant guidelines for children with chronic gastrointestinal symptoms in primary care.

Our choice of a clustered trial design may raise some questions. We chose this approach because it is not feasible to randomise the intervention at an individual level since it would be very demanding for GPs to change their diagnostic strategy for each child. Additionally, it is not desirable to randomise at a GP level due to the risk of contamination between GPs working in the same practice (44). Nevertheless, we concede that the clustered randomised trial design has some limitations (45–47). First, blinding the participating GPs is neither feasible nor desirable because

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the transfer from care as usual to intervention is obvious. To reduce bias, those who perform the analysis will be blinded to the assigned study group. Second, the cluster effect must be considered (40) given that participants within one cluster may share certain characteristics (e.g. quality of care at the GP practice) that could substantially affect power. Therefore, we corrected for the cluster effect in the sample size calculation by using an intraclass correlation coefficient of 0.06, which is higher than used in most cluster trials in primary care (40,48). Finally, this trial design is prone to selection bias (47,49–51), with GPs in the intervention group potentially including participants with different characteristics to those in the control group due to the knowledge gained (e.g. alarm symptoms) in the online training. Although research staff will search for eligible children in the GPs' registration databases to reduce this risk, it should be noted that this process may be prone to the same bias (52).

When designing this study, we used the PRECIS-2 tool to match our design to the intended purpose: a pragmatic yet valid trial (53). We opted for a pragmatic design so that we could reflect the effectiveness of the intervention in routine clinical practice (54). Such trials are also highly generalizable and produce externally valid results that are relevant to decision makers (55–57). However, unlike in explanatory trials, protocol adherence is rarely monitored and the degree to which the intervention is implemented in daily clinical practice often remains uncertain (58). Therefore, any real effect could be masked by a large amount of variation (59). This will be addressed by monitoring whether GPs comply with the protocol and by performing a per protocol analysis.

In conclusion, we seek to evaluate the effect of an FCal-POCT test strategy in children with chronic gastrointestinal symptoms in primary care. If the intervention is shown to be clinically beneficial and cost effective, we will be able to promote its uptake in everyday practice, where we expect it to have a positive impact on children presenting with chronic gastrointestinal symptoms in primary care.

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AUTHORS' CONTRIBUTIONS

GAH, PFR and MYB conceived the original research concept. All authors contributed to the study design. SMA, MPEC and GGB will collect and manage data during the trial. SMA has written and revised this protocol. All authors have contributed important intellectual content to the manuscript and have approved the final version for publication in this journal.

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COMPETING INTERESTS STATEMENT

There are no competing interests to declare.

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FIGURE LEGENDS

Figure 1. Study design

* Secondary outcomes evaluated by questionnaires will only be assessed in children who provide informed consent. We estimate that 50% of the recruited children will provide informed consent.

Figure 2. Test strategy in the intervention group

Legend: Eye inflammation = uveitis, scleritis and episcleritis; FGID = functional gastrointestinal disorders; IBD = inflammatory bowel disease; Skin abnormalities = erythema nodosum, psoriasis and pyoderma gangrenosum.

* Refer to paediatrician if the repeated calprotectin after 1 month is >50 µg/g to prevent diagnostic uncertainty among GPs, parents, and children.

Figure 3. Study timeline at each GP practice

After a GP practice agrees to participate in the study, it is randomised to either the intervention or control group. Shortly thereafter, research staff visits the practice to explain study procedures, which marks the start of the 12-month inclusion period. GPs in the intervention group complete the online training before this visit. Children presenting with chronic gastrointestinal symptoms before the inclusion period starts are not eligible. Follow-up is 6 months for each child.

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SUPPLEMENTARY FILES

Supplementary File 1. Information leaflet control group

Supplementary File 2. Online training modules

Supplementary File 3. Data collection from medical records over 6 months

Supplementary File 4. Relevant International Classification of Primary Care Codes

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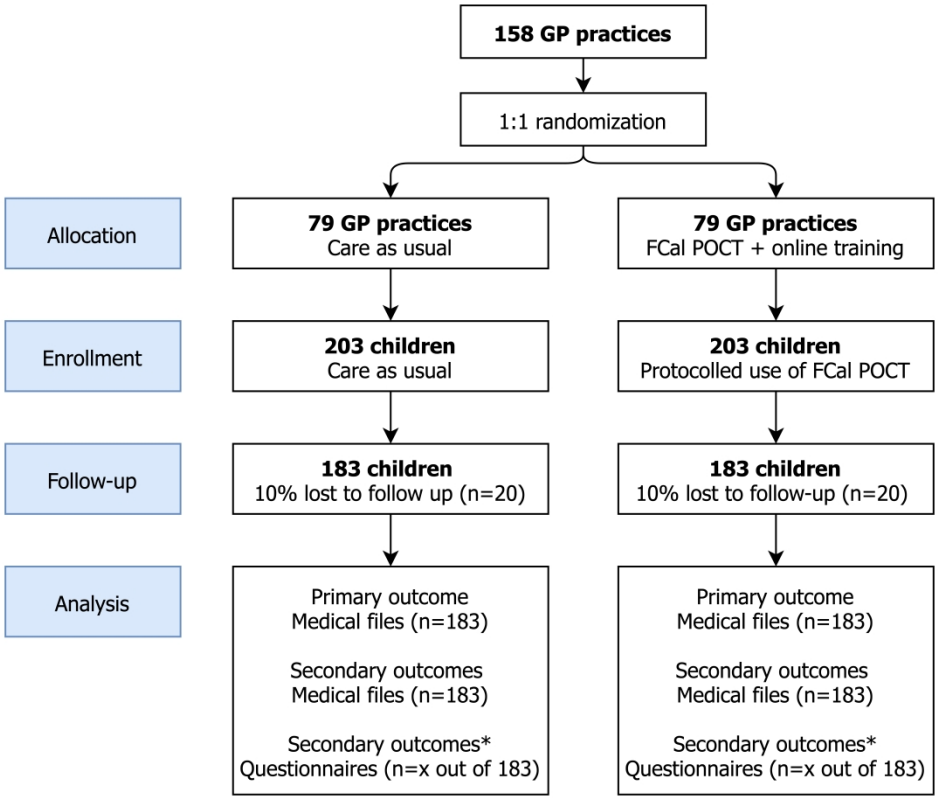

Figure 1. Study design. * Secondary outcomes evaluated by questionnaires will only be assessed in children who provide informed consent. We estimate that 50% of the recruited children will provide informed consent.

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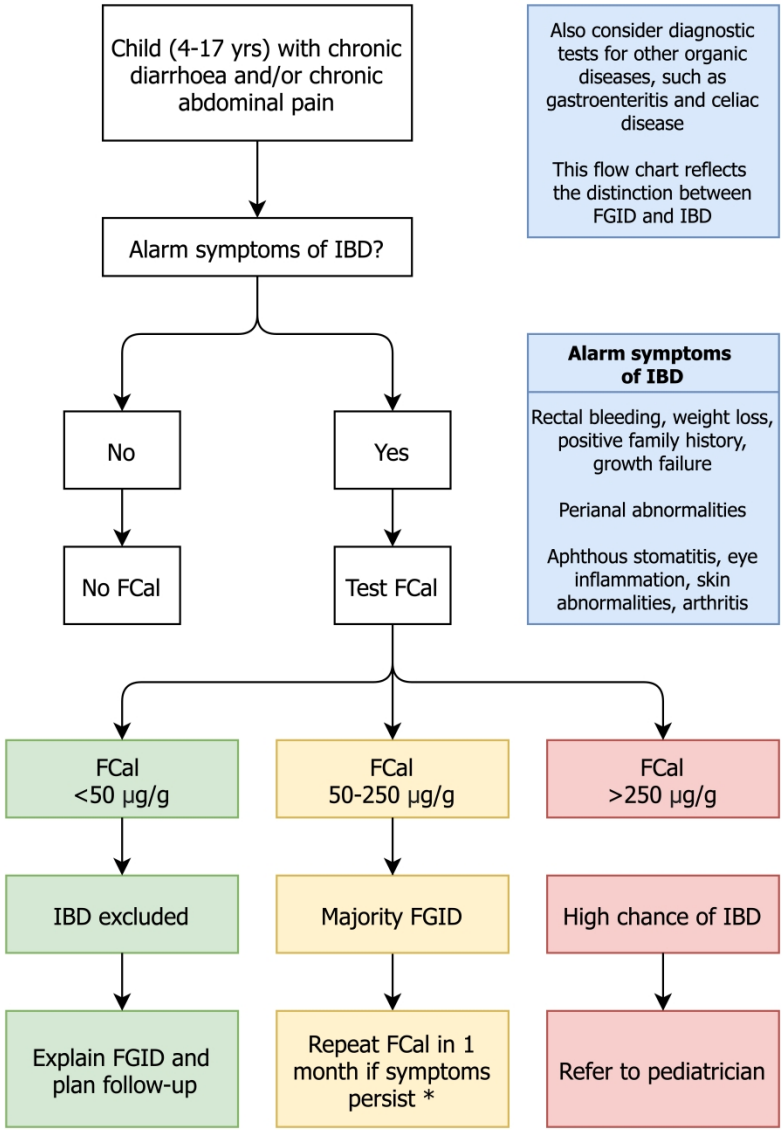

Figure 2. Test strategy in the intervention group. Legend: Eye inflammation = uveitis, scleritis and episcleritis; FGID = functional gastrointestinal disorders; IBD = inflammatory bowel disease; Skin abnormalities = erythema nodosum, psoriasis and pyoderma gangrenosum. * Refer to paediatrician if the repeated calprotectin after 1 month is >50 µg/g to prevent diagnostic uncertainty among GPs, parents, and children.

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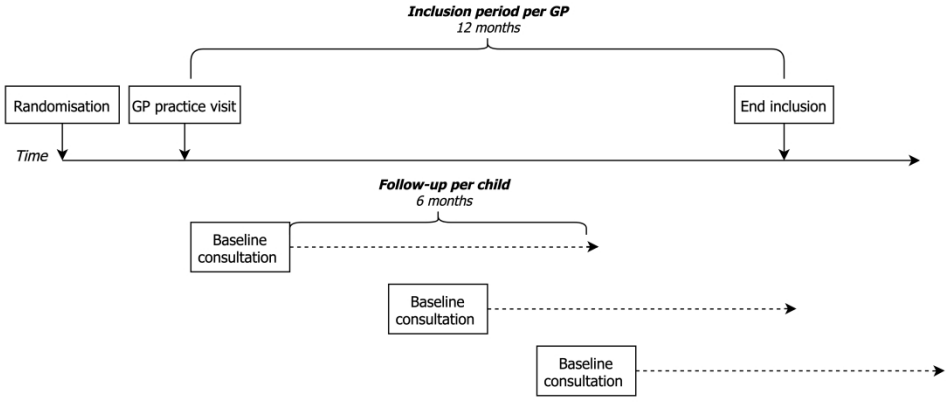

Figure 3. GP and patient timeline. After a GP practice agrees to participate in the study, it is randomised to either the intervention or control group. Shortly thereafter, research staff visits the practice to explain study procedures, which marks the start of the 12-month inclusion period. GPs in the intervention group complete the online training before this visit. Children presenting with chronic gastrointestinal symptoms before the inclusion period starts are not eligible. Follow-up is 6 months for each child.

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Supplementary File 1. Information leaflet control group

Chronic abdominal pain and/or chronic diarrhoea in children 4–18 years in general practice

Epidemiology

90% has functional gastrointestinal disease (FGID). The most frequent disorders are:

- Functional abdominal pain
- Functional constipation
- Irritable bowel syndrome

10% has an organic disorder. The differential diagnosis is age- and gender dependent.

Gastrointestinal disorders

• Parasitic, bacterial and viral gastroenteritis	**prevalence 4.5%**
• Celiac disease	**prevalence 1.5%**
• Crohn's disease and colitis ulcerosa (IBD)	**prevalence <1%**

Non-gastrointestinal disorders

- Girls: dysmenorrhea, sexually transmitted disease, pregnancy
- Familial Mediterranean fever (FMF)

This overview focuses on the gastrointestinal disorders

Medical history

Eating and defecation pattern

Gastrointestinal symptoms

Involuntary weight loss, growth failure, delayed puberty, rectal bleeding

Family history of IBD or celiac disease

Extra intestinal manifestations of IBD: skin abnormalities, arthritis, aphthous stomatitis, eye inflammation

Physical examination

Abdomen: *palpable fecal mass*

Extra intestinal manifestations: *arthritis, skin abnormalities, eye inflammation*

Perianal inspection

Height, weight, BMI

Diagnostic tests

Abdominal pain and diarrhea >10 days	**Fecal culture**
Suspicion of celiac disease	**Anti-TTG**
Suspicion of IBD	**ESR, Hb, leukocytes**

Legend: BMI = body mass index ESR = erythrocyte sedimentation rate; Hb = haemoglobin; IBD = inflammatory bowel disease; TTG = tissue transglutaminase.

Supplementary File 2. Online training modules

1) **Introduction:** The aim of this module is to teach the GP about the differential diagnosis, prevalence, and definitions of chronic gastrointestinal symptoms in children in primary care.
2) **Case 1:** A teenager in whom there is a high suspicion of IBD. This module aims to teach the GP about alarm symptoms for IBD, the diagnostic value of calprotectin (>250 µg/g) and the causes of false-positive results.
3) **Case 2:** A school-aged child with functional abdominal pain. This module aims to teach the GP about the indication for testing, the diagnostic value and the follow-up approach for calprotectin values between 50 and 250 µg/g.
4) **Case 3:** A teenager with chronic abdominal pain and one alarm symptom. This module aims to teach the GP about the diagnostic value of a calprotectin value <50 µg/g and the pros and cons of referral. It also provides tips for communication with a child/parent about FGID.
5) **Proficiency test:** The test includes ten questions that address the key messages of the online training. The GP has three chances to attain seven correct answers.

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Supplementary File 3. Data collection from medical records over 6 months

Variable						
Alarm symptoms for IBD						
Involuntary weight loss	Yes/no	Date				
Growth failure	Yes/no	Date				
Rectal bleeding	Yes/no	Date				
Positive family history for IBD	Yes/no	Date				
Perineal abnormalities	Yes/no	Date				
Aphthous stomatitis	Yes/no	Date				
Eye inflammation	Yes/no	Date				
Arthritis	Yes/no	Date				
Skin abnormalities	Yes/no	Date				
Diagnosis						
GP's diagnosis at index consultation	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
GP's diagnosis at 6 months follow-up	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
Paediatrician's diagnosis at 6 months follow-up	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
Diagnostic tests						
Haemoglobin	Yes/no	Date	Test result			
Leukocytes	Yes/no	Date	Test result			
Thrombocytes	Yes/no	Date	Test result			
CRP	Yes/no	Date	Test result			
ESR	Yes/no	Date	Test result			
Anti-transglutaminase IgA antibody	Yes/no	Date	Test result			
IgA antibody	Yes/no	Date	Test result			
Other blood test	Yes/no	Date	Test result			
Faecal calprotectin POCT	Yes/no	Date	Test result			
Faecal calprotectin sent to laboratory	Yes/no	Date	Test result			
Faecal culture	Yes/no	Date	Test result			
Urine dipstick	Yes/no	Date	Test result			

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Urinalysis	Yes/no	Date	Test result			
Urine culture	Yes/no	Date	Test result			
Abdominal ultrasound	Yes/no	Date	Test result			
X-abdomen	Yes/no	Date	Test result			
Other radiology tests	Yes/no	Date	Test result			
Referral						
Referral	Yes/no	Paediatrician	Ped. gastroenterologist	Physiotherapist	Psychologist	Other
Reason for referral according to GP	*Free text*					
Medication						
Analgesics	Yes/no	Name	Frequency	Dosage	Duration	
Laxatives	Yes/no	Name	Frequency	Dosage	Duration	
Spasmolytics	Yes/no	Name	Frequency	Dosage	Duration	
Antibiotics	Yes/no	Name	Frequency	Dosage	Duration	
Other medication	Yes/no	Name	Frequency	Dosage	Duration	
Consultations						
GP	Yes/no	How often				
Health care use in hospital						
Emergency room	Yes/no	How often				
Use of ambulance	Yes/no	How often				
Endoscopy	Yes/no	Result				
Surgery	Yes/no	Which surgery				
Hospital admission	Yes/no	Duration				

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FGID, functional gastrointestinal disease; GP, general practitioner; IBD, inflammatory bowel disease; IgA, Immunoglobulin A; Ped, paediatric; POCT, point-of-care-test

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Supplementary File 4. Relevant International Classification of Primary Care Codes

D01	Abdominal pain / cramps general
D02	Abdominal pain epigastric
D06	Abdominal pain localised other
D11	Diarrhoea
D12	Constipation
D16	Rectal bleeding
D18	Change in faeces / bowel movements
D27	Fear of digestive disease other
D29	Digestive symptom / complaint other
D93	Irritable bowel syndrome
D99	Disease digestive system other

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Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	See table 2	2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	14 (discussion) 15 (discussion)
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	6 (design and setting)
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5 (design and setting) 6 (intervention and control group)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		NA
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6 (study population)
	4b	Settings and locations where the data were collected		5+6 (design and setting)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	6+7+8 (intervention and control group)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	8+9+10 (outcomes)

	6b	Any changes to trial outcomes after the trial commenced, with reasons		NA
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines		NA
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	6+10
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	10

	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	11+13
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		6
	11b	If relevant, description of the similarity of interventions		NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	11+12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11+12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5+6
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	NA

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)		NA
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		14+15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		NA
Other information				
Registration	23	Registration number and name of trial registry		2 (abstract)
Protocol	24	Where the full trial protocol can be accessed, if available		NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		16

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

REFERENCES

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4/5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

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

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

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Effect of faecal calprotectin testing on referrals for children with chronic gastrointestinal symptoms in primary care: study protocol for a cluster randomised controlled trial

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Effect of faecal calprotectin testing on referrals for children with chronic gastrointestinal symptoms in primary care: study protocol for a cluster randomised controlled trial

S.M. Ansems[1], M.Y. Berger[1], P.F. van Rheenen[2], K.M. Vermeulen[3], G.G. Beugel[1], M.P.E. Couwenberg[1], G.A. Holtman[1]

1. Department of General Practice, University Medical Center Groningen, University of Groningen, the Netherlands
2. Department of Paediatric Gastroenterology, University Medical Center Groningen, University of Groningen, the Netherlands
3. Department of Epidemiology, University Medical Center Groningen, University of Groningen, the Netherlands

Corresponding author: Sophie M. Ansems | Department of General Practice and Elderly Care Medicine, FA21, University of Groningen, University Medical Centre Groningen, PO Box 196, 9700 AD Groningen, The Netherlands | E-mail: s.m.ansems@umcg.nl | +31 6 14186134

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ABSTRACT

Introduction: Children with chronic gastrointestinal symptoms are frequently seen in primary care, yet general practitioners (GPs) often experience challenges distinguishing functional gastrointestinal disorders (FGID) from organic disorders. We therefore aim to evaluate whether a test strategy that includes point-of-care testing (POCT) for faecal calprotectin (FCal) can reduce the referra rate to paediatric specialist care among children with chronic gastrointestinal symptoms. The study findings will contribute to improving the recommendations on FCal use among children in primary care.

Methods and analysis: In this pragmatic cluster randomised controlled trial, we will randomise general practices into intervention and control groups. The intervention group will use FCal-POCT when indicated, after completing online training about its indication, interpretation, and follow-up, as well as communicating an FGID diagnosis. The control group will test and treat according to Dutch GP guidelines, which advise against FCal testing in children. GPs will include children aged 4–18 years presenting to primary care with chronic diarrhoea or recurrent abdominal pain. The primary outcome will be the referral rate for children with chronic gastrointestinal symptoms within 6 months after the initial assessment. Secondary outcomes will be evaluated by questionnaires completed at baseline and at 3- and 6-months' follow-up. These outcomes will include parental satisfaction and concerns, gastrointestinal symptoms, impact of symptoms on daily function, quality of life, proportion of children with paediatrician-diagnosed FGID referred to secondary care, health service use and health care costs. A sample size calculation indicates that we need to recruit 158 GP practices to recruit 406 children.

Ethics and Dissemination: The Medical Research Ethics Committee (MREC) of the University Medical Center Groningen (Netherlands) approved this study (MREC-number: 201900309). The study results will be made available to patients, GPs, paediatricians, and laboratories via peer-reviewed publications and in presentations at (inter)national conferences.

Registration details: The Netherlands Trial Register: NL7690

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Faecal calprotectin (FCal) has high diagnostic value in children in primary care, but it is not known if its use delivers sufficient benefits to patients or if its cost justifies routine use.
- To facilitate optimal FCal use, we believe that training about the indication, interpretation, follow-up and communication of FCal results will be key to introducing this point-of-care test.
- The study results can be directly translated to daily practice in primary care because of its pragmatic design and the incorporation of the test strategy in routine clinical practice.
- Due to this pragmatic design, GPs will not be blinded to either group allocation or study outcomes.
- The cluster design means that we must be aware of the risk of selection bias.

ABBREVATIONS

CONSORT	Consolidated Standards of Reporting Trials
EQ-5D-Y	EuroQol Youth
FCal	Faecal Calprotectin
FDI	Functional Disability Inventory
FGID	Functional gastrointestinal disorders
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
IBD	Inflammatory bowel disease
ICPC	International Classification of Primary Care
MREC	Medical Research Ethics Committee
NHG	*Nederlands Huisartsengenootschap* (Dutch Society of GPs)
POCT	Point-of-care testing
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

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INTRODUCTION

Background and rationale

A Dutch general practitioner (GP) typically sees approximately 10 children with chronic gastrointestinal symptoms each year (1,2). At least 90% of these children will have functional gastrointestinal disorders (FGID) (3). However, before this diagnosis can be made, the GP should ascertain after appropriate medical evaluation that the symptoms cannot be attributed to inflammatory bowel disease (IBD), celiac disease, and other causes (4). However, it is a diagnostic challenge to differentiate between FGID and these organic diseases because their clinical presentations can be very similar. Referring and testing children to identify these low prevalent disorders then delays appropriate treatment for FGID and can lead to unnecessary suffering (5,6). Additionally, we want to prevent specialists' time taken up with FGID, as it is considered a complex and time-consuming problem in specialist care (1). At the same time, it is critical that we avoid delaying the diagnosis and appropriate treatment of IBD and celiac disease to minimise complications such as anaemia and growth failure (7–10), and in the case of IBD, delayed sexual maturation (7), stricturing complications (10) and internal fistulising complications (10–12).

The Dutch Society of General Practitioners (*Nederlands Huisartsen Genootschap*; NHG) recommends testing tissue transglutaminase IgA (tTGA) and total serum IgA for suspected celiac disease and testing haemoglobin, leukocytes and ESR for suspected IBD (13). However, these blood tests cannot exclude IBD, having a sensitivity of only 0.43–0.57 (14–16), and they are invasive and potentially traumatic for children (17). By contrast, faecal calprotectin (FCal) is a non-invasive marker of intestinal inflammation that has been shown in recent observational studies to exclude IBD safely in children with chronic gastrointestinal symptoms and additional alarm symptoms in primary care settings (sensitivity, 0.99–1.00; 95% CI, 0.81–1.00)(18–20). When tested in children without alarm symptoms, however, the positive predictive value decreases due to the low prevalence (<1%) of IBD in this population (21). The number of children referred for further diagnostic evaluation may therefore increase unintentionally.

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However, we emphasize that FCal is especially appropriate for use in primary care due to its high negative predictive value (1.00; 95% CI, 0.94-1.00) rather than its positive predictive value (0.59; 95% CI, 0.41-0.75)(18).

The last decade has seen an increasing focus on point-of-care-testing (POCT) in primary care to improve rapid decision making and triage at the time and place of patient care (22–24). FCal is available as a POCT for which results are available the same day and samples do not need to be sent to a laboratory, yet it retains characteristics that are comparable to the standard laboratory test (25–27). Therefore, the FCal-POCT could decrease a GPs diagnostic uncertainty and provide early reassurance for both parents and children that a potential harmful disease (IBD) can be safely excluded. To optimise FCal-POCT implementation, proper training is needed about its indication, interpretation, and follow-up (22). Perceived parental pressure for a referral is another relevant factor that may influence the decision to refer children with chronic gastrointestinal symptoms. Therefore, GPs must also receive communication skills training to explain the results, the pros and cons of referral, the natural course of (functional) symptoms and when to consult again (28).

Hypothesis

We hypothesise that FCal-POCT, when combined with online training about the indication, interpretation, follow-up of testing and communicating an FGID diagnosis, will increase patient satisfaction and substantially reduce the referral rate for children with chronic gastrointestinal symptoms from primary to secondary care, as compared to usual care.

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METHODS AND ANALYSIS

This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (29) and the extended Consolidated Standards of Reporting Trials (CONSORT) statement for cluster trials (30).

Design and setting

This is a pragmatic clustered randomised controlled trial with 1:1 randomisation, at the level of the GP practice, to either an intervention group or a control group (see Figure 1). From October 2019 to October 2020, GP practices in the Netherlands were invited to participate in the study. The Netherlands has a primary health care system in which the GP functions as the gatekeeper to specialist (i.e., paediatric) care, comparable to the systems in among others Canada and the United Kingdom.

The primary outcome (referral to paediatric specialist care) will be assessed at an individual level within 6 months after baseline GP consultation, defined as the first consultation at which a child meets the criteria for inclusion. The first child was included on October 15th 2019 and the inclusion of children will end once the required sample size is reached (planned October 2021). Six months later is the planned study end date (April 2022)

Study population

Every general practice in the Netherlands is eligible for participation in our study, including all GPs and GP trainees working at those practices. GPs will be asked to include children meeting the following criteria: age 4–18 years; with chronic diarrhoea (defined as soft to watery stool for ≥2 weeks or ≥2 episodes in the past 2 months); and/or with recurrent or chronic abdominal pain (defined as abdominal pain with a recurrent character for ≥2 months or ≥2 episodes in the past 2 months). Children will be excluded if they have a history of chronic organic gastrointestinal disease (e.g. celiac disease or IBD) or if they have had an endoscopic evaluation, referral to paediatric care for gastrointestinal symptoms or an FCal result within the preceding 6 months.

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Intervention and control group

Randomisation and blinding

GP practices will be randomised by a computer-generated list using varying block randomisation in 1:1 ratio by an independent researcher (H van der Worp, PhD) not involved in the project. To reduce the risk of contamination, all GPs working at a given GP practice will be allocated as a cluster in the same study arm. On the rare occasion that a GP works in multiple practices not allocated to the same study arm, this GP will only include children in the practice that first participated in this study. GPs, children, and parents will not be blinded to the intervention, but the research team will be blinded to study group assignment for the statistical analysis.

Control group: care as usual

GPs in the control group will provide care as usual according to the *NHG* guidelines, which recommends not using FCal testing in children (13,31–33). It will nevertheless still be possible for them to request laboratory FCal testing or to refer the child for further diagnostic testing, if deemed necessary. All GPs will receive an information leaflet about what is considered care as usual per the *NHG* guideline (Supplementary File 1).

Intervention group: FCal-POCT plus online training

FCal-POCT devices will be made available to GPs for use in their practices. All participating GPs will complete the obligatory online training and will receive the same information leaflet as the control group. However, this leaflet will be amended to recommend FCal instead of ESR, leukocytes and haemoglobin when IBD is suspected. Although GPs are instructed to only use FCal when the child presents with alarm symptoms (Table 1), FCal use will be at their own discretion. Consequently, children without FCal testing may also be included and GPs may also test and include children with alarm symptoms other than in the online training or children without alarm symptoms.

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The FCal-POCT: IBDoc

The IB*Doc* home testing application (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) will be used. This is an *in vitro* diagnostic immunoassay for quantitatively determining faecal calprotectin in human stool (34). Originally developed for self-testing by trained patients at home, it is also suitable for use in near-patient or laboratory settings (34). In a recent head-to-head comparison of three FCal-POCT devices in children with IBD, the IB*Doc* device had the best agreement with ELISA and produced significantly fewer reading errors compared with the other FCal-POCT devices (27). In the intervention group, trained research staff will teach GP assistants to use the IB*Doc* device during a 60-minute face-to-face training session.

Online training for GPs

The content of the training was developed during two expert panel sessions with two academic paediatric gastroenterologists (PFR), two GPs (MYB and MPEC), a psychologist, an educationalist, a clinical epidemiologist (GAH) and a clinical chemist. In the first session, we formulated the FCal-POCT test strategy based on a review of the scientific literature (1,3,14,18,19,27). In the second session, the concept of the online training was adjusted according to the four domains of Kirkpatrick's model: reaction, learning, behaviour and results (35). Subsequently, the research team developed the online training (including video recordings) in close collaboration with the expert panel. The online training was tested by five GPs (academic and non-academic) before implementation.

The final 60-minute online training for GPs reflects the FCal-POCT test strategy. It has been shown that an FCal value <50 µg/g can safely exclude IBD in children in primary care (sensitivity of 0.99–1.00 [95% CI 0.81–1.00]) (18,19). Additionally, an FCal value >250 µg/g has a specificity of 0.98 (95% CI 0.92–0.99) (18). However, an FCal value >50 µg/g also has a high false-positive rate (13%) when tested in a population of children both with and without alarm symptoms (18,36). Therefore, it is recommended to test only those children with alarm symptoms (Table 1), to monitor those with an FCal value of 50–250 µg/g and to refer those with an FCal value >250 µg/g.

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In addition to the indication and interpretation of cut off values, the online training includes detail on the follow-up of test results between 50 and 250 µg/g, how to communicate the FCal result and how to educate about FGID (14,37). Figure 2 shows the flow chart for the test strategy. This features prominently throughout the online training and is given to GPs as a desk reminder. The online training contains five modules in total: an introduction module, three modules each covering a different patient case or test scenario, and a module with a proficiency test (Supplementary File 2). The online training uses text blocks, tables, graphs, images, videos (GP consultations with a child and parent) and interactive questions.

Outcomes

Primary outcome

The primary outcome is the proportion of referrals to secondary care within 6 months after the baseline consultation. Research staff will extract this information from the medical files of GPs.

Secondary outcomes

Parental satisfaction about baseline consultation

The Parental Medical Interview Scale (P-MISS) measures parent satisfaction with the GP consultation (38). This questionnaire assesses physician communication with the parent and child, distress relief, and adherence intent on a five-point Likert scale ranging from 'strongly disagree' (score = 1) to 'strongly agree' (score = 5). The questionnaire showed good construct validity and internal consistency ($\alpha = 0.86$) (38,39).

Parental concern at baseline and at 3 and 6 months

At the baseline consultation and after 3 and 6 months, parents will answer the question 'How concerned do you feel about your child's gastrointestinal symptoms?' on a numeric version of a visual analogue scale (scored 1 to 10, with 1 defined as 'not concerned' and 10 defined as 'extremely concerned'). At the baseline consultation, parents will complete an additional questionnaire about their concerns. This will cover if and where parents sought advice before

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contacting their physician, what their current concerns are, and how the physician could provide reassurance to both the parent and child (40).

Self-reported gastrointestinal symptoms at baseline and at 3 and 6 months

Self-reported gastrointestinal symptoms will be evaluated using a ten-item questionnaire that we have previously used in a study of the diagnostic value of FCal for IBD in primary care (41). This questionnaire assesses the presence of alarm symptoms, as well as the duration and severity of abdominal pain and/or diarrhoea.

Impact of gastrointestinal symptoms on the child's daily function at baseline and at 3 and 6 months

The impact of symptoms on daily function will be evaluated with the Functional Disability Inventory (FDI) (42). This assesses self-reported difficulty in physical and psychosocial functioning due to physical health over the past 2 weeks. Responses to 15 items are scored on five-point scales that range from 'no trouble' (0) to 'impossible' (4). Items are averaged to give a composite score. Cronbach's alpha coefficient for the FDI is reported to be 0.90 (42).

Child's quality of life at baseline and at 3 and 6 months

Quality of life will be evaluated with the EuroQol Youth (EQ-5D-Y), a generic measure for quality of life. This instrument includes five domains (i.e. mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) with three levels of severity (i.e. no problems, some problems, and a lot of problems) (43). The questionnaire is feasible for use by children (44).

The proportion of children referred to paediatric care with FGID over 6 months

The proportion of children diagnosed with FGID by the paediatrician will be recorded among those referred to paediatric care. This information will be extracted from the child's medical records based on letters sent by the paediatrician to the GP.

Health care use over 6 months

For all children, we will collect the following data from medical records: diagnostic tests, referrals to health care providers other than a paediatrician, medication prescriptions, GP consultation

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frequency and health care use at hospital (Supplementary File 3). For FCal in specific, we will also collect whether children return their stool samples.

Costs over 6 months

Units of medical consumption will be extracted from medical records for all children (see health care use). In addition, cost questionnaires will be completed by parents at baseline and at 3- and 6-months' follow-up. These will measure additional health care use, out-of-pocket expenses and productivity losses (absence from work) based on adapted versions of the iMCQ and the iPCQ (45).

Recruitment

We will invite all GP practices connected to the Academic General Practitioner Development Network (AHON; *Academisch Huisarts Ontwikkel Netwerk*) via an informational letter. This network comprises 473 urban and rural GP practices in the four northern provinces of the Netherlands, and it seeks to facilitate collaboration in research, education, and innovation in general practice. We will also approach GP practices throughout the Netherlands with which our research staff are connected.

GPs will identify and recruit consecutive eligible children during baseline consultations for one year (Figure 3). Additionally, research staff will retrospectively search for eligible children seen in practice in the previous 3 months. They will search in GP registration databases using a search strategy based on International Classification of Primary Care (ICPC) codes (Supplementary File 4). All included children and/or parents (regardless of the recruitment strategy) will receive a patient information letter and will be asked to provide informed consent for completing questionnaires (Supplementary File 5). Consequently, secondary outcomes assessed with questionnaires will only be evaluated in children who provide this consent.

Data collection

For each eligible child, independent of inclusion during or after consultation, the GP will complete a trial inclusion form detailing the inclusion/exclusion criteria, gender, date of birth, presence of alarm symptoms and use of FCal-POCT (the latter only in the intervention group).

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The trial inclusion form will be sent to the researchers, and for all included children, data will be retrieved from their medical files for each consultation (including baseline) over a 6-month follow-up period by the research team in a standardized online data-entry form (Supplementary File 3). Children and/or parents who provide informed consent will also complete digital questionnaires via RedCap after consultations at baseline, 3 months and 6 months. The estimated time to complete each questionnaire is 15–20 minutes, and if they are not completed, the child and/or parents will automatically receive reminders via e-mail after 7 and 14 days. If not completed after two reminders, we will call the child and/or parents by phone.

Sample size

Based on our earlier study on the diagnostic value of FCal in primary care (18), as well as the cross-sectional study on the management of children with abdominal pain in primary care (3), we expect referrals of children with chronic gastrointestinal symptoms to reduce from 17% to 7%. To detect this difference with a power of 80% and a significance level of 5%, an individually randomised study would need 326 children (163 per arm). Given a mean cluster size (expected recruitment rate per practice) of 3 and an intraclass correlation coefficient of 0.06 (28,46), we would need 366 children (183 per arm). Then, allowing for a loss to follow-up of 10%, this increases to 406 children (203 per arm) from 134 general practices (67 per arm). We assume that 15% of the practices will not recruit any children; therefore, we aim to recruit 158 general practices (79 per arm).

Analysis

We will use descriptive statistics to summarise the data of GPs and children in the intervention and control groups, starting with their baseline characteristics. All analyses will be presented as estimates of intervention effects (adjusted mean differences or odds ratios, as appropriate), with associated 95% CIs and *p* values. Analysis for both the primary and secondary outcomes will initially be done on an intention-to-treat basis, with children analysed within the GP group in which they are registered, irrespective of the care received. Analyses will then be repeated for

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both the primary and secondary outcomes on a per protocol basis. In the intervention group, we will only include children who receive the intended diagnostic strategy (per the indications explained in the online training and with a returned stool sample) or rightfully did not receive FCal testing (without alarm symptoms) and in the control group, we will only include children who did not undergo FCal testing. We will analyse the primary outcome by multilevel logistic regression modelling to account for the practice. The effect of the intervention on secondary parameters will be assessed by multilevel logistic (dichotomous variables) or linear (continuous variables) regression modelling, as appropriate.

Economic evaluation

Alongside the RCT, we will perform a cost-effectiveness study with two aims. The primary aim will be to study the incremental costs of FCal-POCT compared to care as usual from a societal perspective. If the new test strategy reduces the number of referrals, this will be visible as a cost reduction in the economic evaluation. An incremental cost-utility ratio will then be calculated, based on the EQ-5D-Y for assessing utility. The secondary aim will be to estimate the cost-effectiveness of FCal-POCT. Two incremental cost-effectiveness ratios will be calculated, using parental concern and parental satisfaction as effect parameters. Costs will be measured from a societal perspective, such that productivity losses incurred by parents will also be included. Health care consumption will be valued according to Dutch standard guidelines for economic evaluations (47). Bootstrap re-sampling will be performed on the costs (primary analysis) and on the cost–effect pairs (cost-effectiveness and cost-utility) to produce confidence intervals. Finally, cost-effectiveness planes and acceptability curves will be plotted.

Patient and public involvement

We have collaborated with the Foundation Child and Hospital (*Stichting Kind en Ziekenhuis*) and have incorporated their opinions and expertise in the grant proposal, patient information letters and recruitment strategies. Moreover, we will ask them to help disseminate the study results to the public. In addition, we will distribute the study results to participating children and/or

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parents via a short e-mail newsletter. The Dutch Gastroenterology and Hepatology Foundation supports our research question and will also be involved in the dissemination of results.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The Medical Research Ethics Committee (MREC) of the University Medical Center Groningen (Netherlands) (MREC-number: 201900309) approved this study. The ethics committee waived the requirement to obtain written informed consent for collecting data from patients' medical files, according to Dutch law (Medical Treatment Contracts Act). This was allowed because asking for written informed consent from children and/or their parents could jeopardise recruitment. Additionally, it will reduce the risk of selection bias and increase the generalizability of our results to a real-world setting. For the assessment of secondary outcomes by questionnaires, informed consent will be obtained either from parents alone (child <12 years), parents and child (child 12–15 years) or the child alone (>15 years), consistent with Dutch law. Additionally, all participating GP practices will be required to sign a studyagreement consenting to study protocol adherence and data collection by researchers from medical files. Important protocol changes will be communicated to the ethics committee and participating practices.

Dissemination

We aim to embed our study results in clinical practice. The findings will therefore be made available to patients, GPs, paediatricians, and laboratories via presentations at national and international conferences, social media, and peer-reviewed publications, irrespective of the magnitude or direction of effect. Within current national and international guidelines, there is a knowledge gap about the use of FCal in children in primary care. As such, our results will provide high quality evidence according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria because we include the impact on patient-important outcomes (48). The data of this study will be available on request.

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DISCUSSION

To the best of our knowledge, this is the first trial designed to evaluate the effect of using FCal in the diagnostic process of GPs and how this affects referral rates for children with chronic gastrointestinal symptoms. We assume that children and/or parents in the intervention group will have improved patient-important outcomes due to the reduced diagnostic uncertainty. As such, we hypothesise that the referral rate will decrease. Although additional costs will be incurred by using FCal-POCT in the intervention group, we expect total costs to be lower compared to usual care because of the reduced use of other health care services (e.g. fewer GP consultations, blood tests and referrals), as well as less productivity loss for parents.

There is increasing awareness that new medical tests should have scientifically proven patient benefits before they are implemented in health care guidelines. In 2014, Horvath et al. described a new cyclical framework for evaluating in vitro medical tests, and this consisted of analytical and clinical performance, clinical and cost-effectiveness, and broader impact (49). The first step in Horvath's framework, analytical and clinical performance, has already been evaluated for FCal-POCT (18,25). In this trial, we will evaluate the impact of the test in daily practice, focusing on its clinical effectiveness and cost-effectiveness. An additional qualitative study is also needed to evaluate the broader impact of the FCal-POCT in primary care among GPs, GP assistants, parents, and children. If our hypothesis is confirmed, we anticipate that there may be sufficient evidence to include a recommendation on the use of FCal-POCT in relevant guidelines for children with chronic gastrointestinal symptoms in primary care.

Our choice of a clustered trial design may raise some questions. We chose this approach because it is not feasible to randomise the intervention at an individual level since it would be very demanding for GPs to change their diagnostic strategy for each child. Additionally, it is not desirable to randomise at a GP level due to the risk of contamination between GPs working in the same practice (50). Nevertheless, we concede that the clustered randomised trial design has some limitations (51–53). First, blinding the participating GPs is neither feasible nor desirable because

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the transfer from care as usual to intervention is obvious. To reduce bias, those who perform the analysis will be blinded to the assigned study group. Second, the cluster effect must be considered (46) given that participants within one cluster may share certain characteristics (e.g. quality of care at the GP practice) that could substantially affect power. Therefore, we corrected for the cluster effect in the sample size calculation by using an intraclass correlation coefficient of 0.06, which is higher than used in most cluster trials in primary care (46,54). Finally, this trial design is prone to selection bias (53,55–57), with GPs in the intervention group potentially including participants with different characteristics to those in the control group due to the knowledge gained (e.g. alarm symptoms) in the online training. Although research staff will search for eligible children in the GPs' registration databases to reduce this risk, it should be noted that this process may be prone to the same bias (58).

When designing this study, we used the PRECIS-2 tool to match our design to the intended purpose: a pragmatic yet valid trial (59). We opted for a pragmatic design so that we could reflect the effectiveness of the intervention in routine clinical practice (59). Such trials are also highly generalizable and produce externally valid results that are relevant to decision makers (60–62). However, unlike in explanatory trials, protocol adherence is rarely monitored and the degree to which the intervention is implemented in daily clinical practice often remains uncertain (63). Therefore, any real effect could be masked by a large amount of variation (64). This will be addressed by monitoring whether GPs comply with the protocol and by performing a per protocol analysis.

This study evaluates the impact of a test strategy in which FCal testing is a major component. It will be impossible to distinguish whether a possible effect can be attributed to FCal testing or to the training. However, we think that these two elements should go hand-in-hand in order to increase the compliance to the new test strategy and prevent missed diagnoses, over-diagnosis and unnecessary costs for patients and wider society (22,65). This is of similar importance when a test is implemented in a real world setting.

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In a consensus meeting with pediatricians and GPs we selected the alarm symptoms for IBD with the highest discriminatory power. We are of the opinion that adding less discriminating alarm symptoms will unintentionally increase the number of false positive findings.

In conclusion, we seek to evaluate the effect of an FCal-POCT test strategy in children with chronic gastrointestinal symptoms in primary care. If the intervention is shown to be clinically beneficial and cost effective, we will be able to promote its uptake in everyday practice, where we expect it to have a positive impact on children presenting with chronic gastrointestinal symptoms in primary care.

AUTHORS' CONTRIBUTIONS

GAH, PFR, KMV and MYB conceived the original research concept. All authors contributed to the study design. SMA, MPEC and GGB will collect and manage data during the trial. SMA has written and revised this protocol. All authors have contributed important intellectual content to the manuscript and have approved the final version for publication in this journal.

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COMPETING INTERESTS STATEMENT

There are no competing interests to declare.

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Table 1. Definitions of alarm symptoms for Inflammatory Bowel Disease

Alarm symptom	**Method of ascertainment**	**Definition of positive finding**
Positive family history for IBD	History	Affected first-degree relative(s)
Rectal bleeding	History	
Involuntary weight loss	History + physical examination	
Decreased growth velocity	History + physical examination	
Aphthous stomatitis	History + physical examination	
Arthritis	History + physical examination	
Eye inflammation	History + physical examination	Uveitis, (epi) scleritis
Skin abnormalities	Physical examination	Pyoderma gangrenosum, psoriasis, erythema nodosum
Perianal abnormalities	Physical examination	Skin tags, perianal fistulas, haemorrhoids, perianal fissures, perianal abscesses

These definitions apply to the alarm symptoms mentioned in the protocol, figures and all supplementary files.
IBD; Inflammatory Bowel Disease.

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FIGURE LEGENDS

Figure 1. Study design

* Secondary outcomes evaluated by questionnaires will only be assessed in children who provide informed consent. We estimate that 50% of the recruited children will provide informed consent.

Figure 2. Test strategy in the intervention group

[a] Per definitions in Table 1.

[b] Refer to paediatrician if the repeated calprotectin after 1 month is >50 µg/g to prevent diagnostic uncertainty among GPs, parents, and children.

Figure 3. Study timeline at each GP practice

After a GP practice agrees to participate in the study, it is randomised to either the intervention or control group. Shortly thereafter, research staff visits the practice to explain study procedures, which marks the start of the 12-month inclusion period. GPs in the intervention group complete the online training before this visit. Children presenting with chronic gastrointestinal symptoms before the inclusion period starts are not eligible. Follow-up is 6 months for each child.

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SUPPLEMENTARY FILES

Supplementary File 1. Information leaflet control group

Supplementary File 2. Online training modules

Supplementary File 3. Data collection from medical records over 6 months

Supplementary File 4. Relevant International Classification of Primary Care Codes

Supplementary File 5. Consent forms

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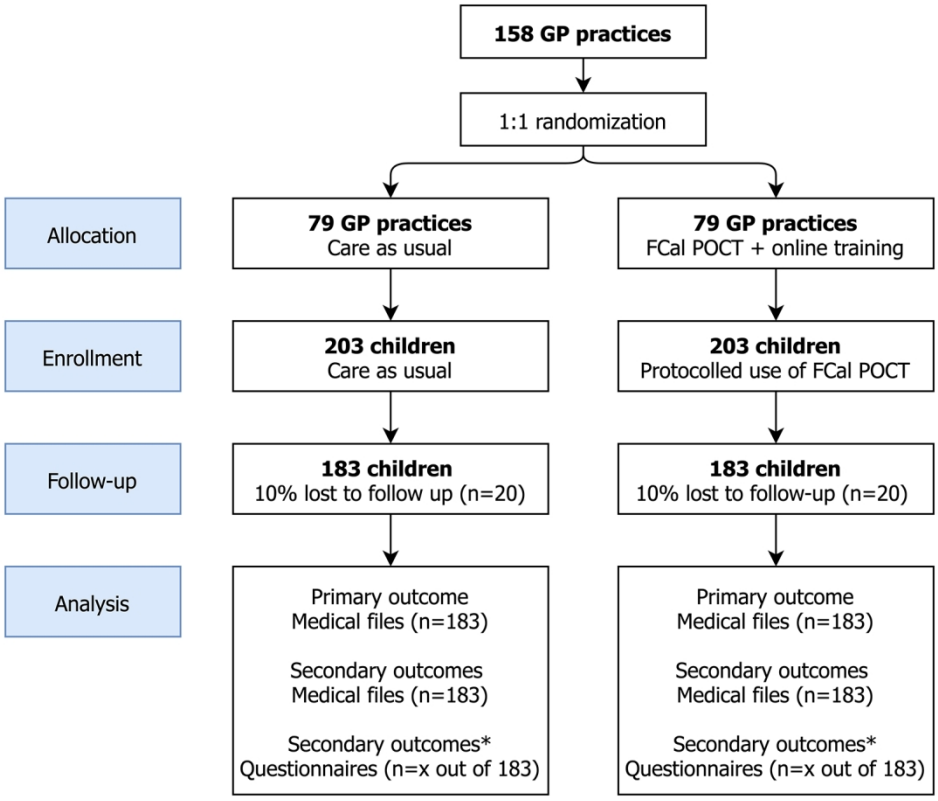


Figure 1. Study design. * Secondary outcomes evaluated by questionnaires will only be assessed in children who provide informed consent. We estimate that 50% of the recruited children will provide informed consent.

145x124mm (300 x 300 DPI)

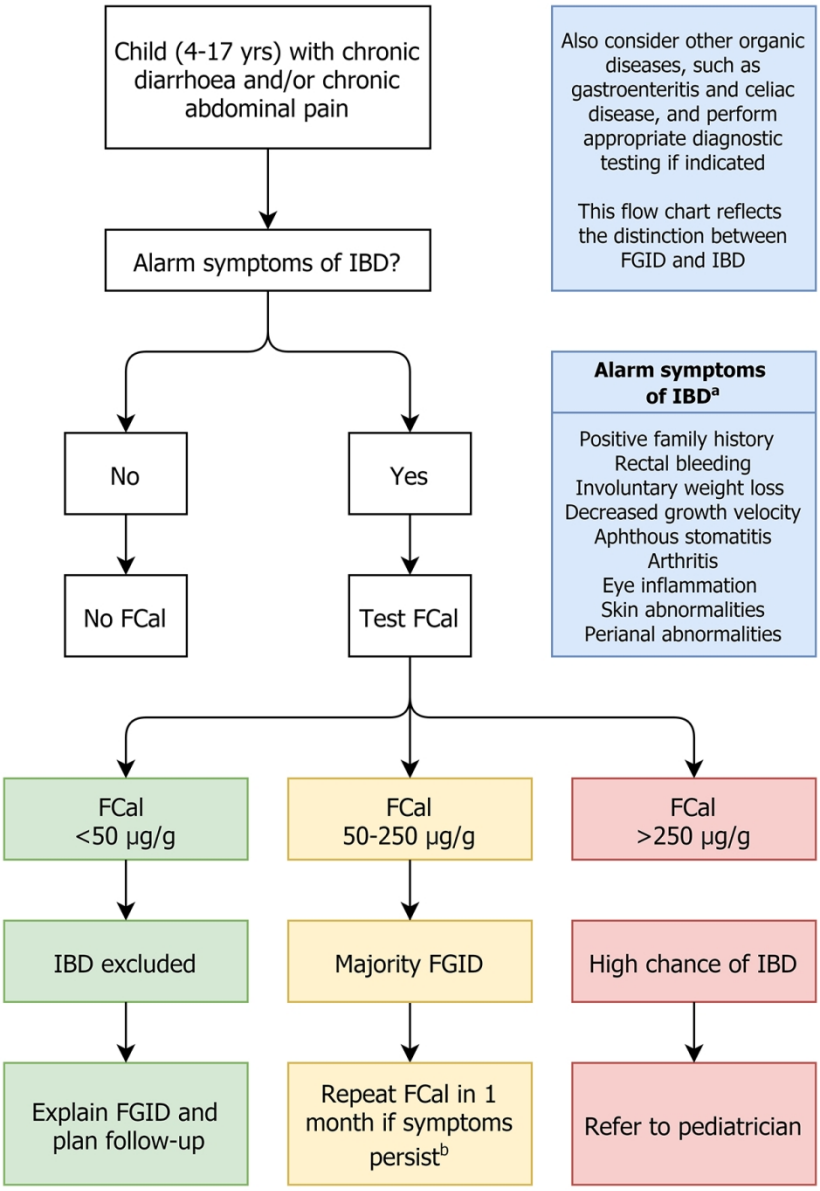
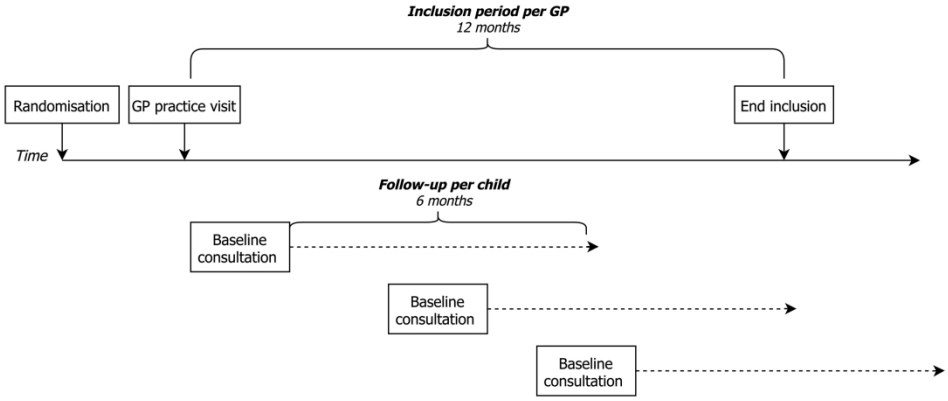


Figure 2. Test strategy in the intervention group. [a] Per definitions in Table 1. [b] Refer to paediatrician if the repeated calprotectin after 1 month is >50 µg/g to prevent diagnostic uncertainty among GPs, parents, and children.

104x150mm (300 x 300 DPI)



GP and patient timeline. After a GP practice agrees to participate in the study, it is randomised to either the intervention or control group. Shortly thereafter, research staff visits the practice to explain study procedures, which marks the start of the 12-month inclusion period. GPs in the intervention group complete the online training before this visit. Children presenting with chronic gastrointestinal symptoms before the inclusion period starts are not eligible. Follow-up is 6 months for each child.

205x91mm (300 x 300 DPI)

Supplementary File 1. Information leaflet control group

Chronic abdominal pain and/or chronic diarrhoea in children 4–18 years in general practice

Epidemiology

90% has functional gastrointestinal disease (FGID). The most frequent disorders are:

- Functional abdominal pain
- Functional constipation
- Irritable bowel syndrome

10% has an organic disorder. The differential diagnosis is age and gender dependent.

Gastrointestinal disorders

• Parasitic, bacterial and viral gastroenteritis	**prevalence 4.5%**
• Celiac disease	**prevalence 1.5%**
• Crohn's disease and colitis ulcerosa (IBD)	**prevalence <1%**

Non-gastrointestinal disorders

- Girls: dysmenorrhea, sexually transmitted disease, pregnancy
- Familial Mediterranean fever (FMF)

This overview focuses on the gastrointestinal disorders

Medical history

Eating and defecation pattern

Gastrointestinal symptoms

Alarm symptoms[a]

Positive family history for IBD or celiac disease

Rectal bleeding, involuntary weight loss, decreased growth velocity

Aphthous stomatitis, arhthritis, eye inflammation

Physical examination

Abdomen: *palpable fecal mass*

Alarm symptoms[a]

Involuntary weight loss, decreased growth velocity

Ahpthous stomatitis, arthritis, eye inflammation, skin abnormalities

Perianal abnormalities

Diagnostic tests

Abdominal pain and diarrhea >10 days	**Fecal culture, fecal ova and parasite test**
Suspicion of celiac disease	**tTGA, total serum IgA**
Suspicion of IBD	**ESR, Hb, leukocytes**

[a] Per definitions in Table 1.

Legend: BMI = body mass index ESR = erythrocyte sedimentation rate; Hb = haemoglobin; IBD = inflammatory bowel disease; IgA = Immunoglobulin A; tTGA = tissue transglutaminase IgA antibody

Supplementary File 2. Online training modules

1) **Introduction:** The aim of this module is to teach the GP about the differential diagnosis, prevalence, and definitions of chronic gastrointestinal symptoms in children in primary care.
2) **Case 1:** A teenager in whom there is a high suspicion of IBD. This module aims to teach the GP about alarm symptoms for IBD, the diagnostic value of calprotectin (>250 µg/g) and the causes of false-positive results.
3) **Case 2:** A school-aged child with functional abdominal pain. This module aims to teach the GP about the indication for testing, the diagnostic value and the follow-up approach for calprotectin values between 50 and 250 µg/g.
4) **Case 3:** A teenager with chronic abdominal pain and one alarm symptom. This module aims to teach the GP about the diagnostic value of a calprotectin value <50 µg/g and the pros and cons of referral. It also provides tips for communication with a child/parent about FGID.
5) **Proficiency test:** The test includes ten questions that address the key messages of the online training. The GP has three chances to attain seven correct answers.

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Supplementary File 3. Data collection from medical records over 6 months

Variable						
Alarm symptoms for IBD [a]						
Positive family history for IBD	Yes/no	Date				
Rectal bleeding	Yes/no	Date				
Involuntary weight loss	Yes/no	Date				
Decreased growth velocity	Yes/no	Date				
Aphthous stomatitis	Yes/no	Date				
Arthritis	Yes/no	Date				
Eye inflammation	Yes/no	Date				
Skin abnormalities	Yes/no	Date				
Perianal abnormalities	Yes/no	Date				
Diagnosis						
GP's diagnosis at index consultation	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
GP's diagnosis at 6 months follow-up	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
Paediatrician's diagnosis at 6 months follow-up	FGID	Constipation	Gastroenteritis	IBD	Celiac disease	Other
Diagnostic tests						
Haemoglobin	Yes/no	Date	Test result			
Leukocytes	Yes/no	Date	Test result			
Thrombocytes	Yes/no	Date	Test result			
CRP	Yes/no	Date	Test result			
ESR	Yes/no	Date	Test result			
Anti-transglutaminase IgA antibody	Yes/no	Date	Test result			
IgA antibody	Yes/no	Date	Test result			
Other blood test	Yes/no	Date	Test result			
Faecal calprotectin POCT	Yes/no	Date	Test result			
Faecal calprotectin sent to laboratory	Yes/no	Date	Test result			
Faecal culture	Yes/no	Date	Test result			
Faecal ova and parasite test	Yes/no	Date	Test result			

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Urine dipstick	Yes/no	Date	Test result			
Urinalysis	Yes/no	Date	Test result			
Urine culture	Yes/no	Date	Test result			
Abdominal ultrasound	Yes/no	Date	Test result			
X-abdomen	Yes/no	Date	Test result			
Other radiology tests	Yes/no	Date	Test result			
Referral						
Referral	Yes/no	Paediatrician	Ped. gastroenterologist	Physiotherapist	Psychologist	Other
Reason for referral according to GP	*Free text*					
Medication						
Analgesics	Yes/no	Name	Frequency	Dosage	Duration	
Laxatives	Yes/no	Name	Frequency	Dosage	Duration	
Spasmolytics	Yes/no	Name	Frequency	Dosage	Duration	
Antibiotics	Yes/no	Name	Frequency	Dosage	Duration	
Other medication	Yes/no	Name	Frequency	Dosage	Duration	
Consultations						
GP	Yes/no	How often				
Health care use in hospital						
Emergency room	Yes/no	How often				
Use of ambulance	Yes/no	How often				
Endoscopy	Yes/no	Result				
Surgery	Yes/no	Which surgery				
Hospital admission	Yes/no	Duration				

[a] Per definitions in Table 1.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FGID, functional gastrointestinal disease; GP, general practitioner; IBD, inflammatory bowel disease; IgA, Immunoglobulin A; Ped, paediatric; POCT, point-of-care-test

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Supplementary File 4. Relevant International Classification of Primary Care Codes

D01	Abdominal pain / cramps general
D02	Abdominal pain epigastric
D06	Abdominal pain localised other
D11	Diarrhoea
D12	Constipation
D16	Rectal bleeding
D18	Change in faeces / bowel movements
D27	Fear of digestive disease other
D29	Digestive symptom / complaint other
D93	Irritable bowel syndrome
D99	Disease digestive system other

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Supplementary File 5. Consent Forms

CONSENT FORM PARTICIPANTS

For participants aged 12 – 17 years*

I have been asked to give consent for participation in this medically scientific research.

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether I want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my participation without providing a reason.
- I give consent to collect and use my data for the purposes mentioned in the patient information letter.
- I know that some persons can look at my data. These persons are mentioned in the patient information letter.
- I agree to participate in this research.

Please tick the boxes:

☐ I give consent to use my data for a maximum of 15 years for comparable scientific research in the future.

☐ I give consent to be approached for future research.

Please fill in:

First and last name _____

Date of birth _____

E-mail address _____

Phone number _____

GP _____

Date _____ Signature _____

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

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CONSENT FORM PARENTS/GUARDIANS

For parents of participants aged 4 – 15 years

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

- I have read the patient information letter. It was possible to ask questions. My questions are sufficiently answered. I had enough time to decide whether me and my child want to participate.
- I know that my participation is voluntary. I know I can decide at any moment to end my child's participation without providing a reason.
- I give consent to collect and use my child's data for the purposes mentioned in the patient information letter.
- I know that some persons can look at my child's data. These persons are mentioned in the patient information letter.
- I agree that me and my child participate in this research.

Please tick the boxes:

☐ I give consent to use my data for a maximum of 15 years for comparable scientific research in the future.

☐ I give consent to be approached for future research.

Please fill in:

Child's first and last name	_____
Child's date of birth	_____
GP	_____

	Parent/guardian 1 *	Parent/guardian 2 *
Name	_____	_____
Date	_____	_____
Signature		
E-mail	_____	_____
Phone	_____	_____

Please tick one of the boxes below

☐ There is joint parental authority and both parents have signed this form
☐ There is joint parental authority and I have notified the other parent/guardian
☐ There is no joint parental authority but there is one-headed authority

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

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

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

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4/5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

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

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

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Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	See table 2	2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	14 (discussion) 15 (discussion)
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	6 (design and setting)
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5 (design and setting) 6 (intervention and control group)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		NA
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6 (study population)
	4b	Settings and locations where the data were collected		5+6 (design and setting)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	6+7+8 (intervention and control group)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	8+9+10 (outcomes)

	6b	Any changes to trial outcomes after the trial commenced, with reasons		NA
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines		NA
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	6+10
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	10

	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	11+13
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		6
	11b	If relevant, description of the similarity of interventions		NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	11+12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11+12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5+6
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	NA

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)		NA
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		14+15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		NA
Other information				
Registration	23	Registration number and name of trial registry		2 (abstract)
Protocol	24	Where the full trial protocol can be accessed, if available		NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		16

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

REFERENCES