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Efficacy of anti-TNF dosing interval lengthening in adolescents and young adults with inflammatory bowel disease in sustained remission (FREE-study): protocol for a partially randomised patient preference trial

Marleen Bouhuys ,[1] Willem S Lexmond,[1] Gerard Dijkstra,[2] Triana Lobatón,[3] Edouard Louis,[4] Stephanie van Biervliet,[5] Henk Groen ,[6] Jordi Guardiola,[7] Patrick van Rheenen [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Patrick van Rheenen; p.f.van.rheenen@umcg.nl

ABSTRACT

Introduction Anti-tumour necrosis factor (TNF) therapy has greatly improved treatment outcomes in patients with inflammatory bowel disease (IBD), but long-term use is associated with cutaneous reactions, susceptibility to infections and frequent injections or hospital visits. Several non-controlled studies have demonstrated that dose reduction is feasible for a subset of patients, provided that early detection of a disease flare is possible. Here, we aim to compare the effectiveness of interval lengthening with standard dosing in maintaining remission in young patients with IBD.

Methods and analysis In this international, prospective, non-inferiority, partially randomised patient preference trial, we aim to recruit 148 patients aged 12–25 years with luminal Crohn's disease or ulcerative colitis in sustained remission (ie, three consecutive in-range faecal calprotectin (FC) results or recently confirmed endoscopic remission). In the interventional arm, the dosing interval will be lengthened from 8 to 12 weeks for infliximab users and from 2 to 3 weeks for adalimumab users. In the control group, standard dosing will be continued. Rapid tests will be performed for FC every 4 weeks and for anti-TNF trough levels every 12 weeks. The primary outcome is the cumulative incidence of out-of-range FC results at 48-week follow-up. Secondary endpoints include time to get out-of-range FC results, cumulative incidence of adverse effects, proportion of patients progressing to loss of response and identification of predictors of successful interval lengthening.

Ethics and dissemination The protocol has been approved by the Medical Ethics Review Committee of the University Medical Centre Groningen and is pending at the other participating centres. Results will be disseminated in peer-reviewed journals and presented at scientific meetings.

Trial registration number EudraCT number: 2020-001811-26; ClinicalTrials.gov Identifier: NCT04646187. Protocol version 4, date 17 September 2021.

Strengths and limitations of this study

- This is the first prospective, interventional study to evaluate the feasibility of anti-tumour necrosis factor (TNF) dosing interval lengthening in a cohort of adolescents and young adults with inflammatory bowel disease.
- Potential harm of interval lengthening (lower anti-TNF trough levels leading to pharmacokinetic loss of response) is minimised by 4-weekly monitoring of faecal calprotectin levels, which will detect an imminent flare at an early stage and thus allows proactive reversal to the original dosing interval.
- The partially randomised, patient preference design accommodates the patients (and their parents) with a strong preference for either interval lengthening or standard dosing.
- We acknowledge that the inclusion of non-randomised patients creates a cohort study alongside a randomised controlled trial, which could compromise internal validity. Separate analyses of baseline characteristics and outcomes for both subsets of patients will reveal whether bias has occurred.

INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are immune-mediated chronic relapsing disorders that often begin in adolescence or early adulthood. In both CD and UC, the disease is characterised by bouts of inflammation (relapses or flares) and periods of remission. Active inflammation that goes untreated results in irreversible bowel damage for which intestinal surgery may be required.

In the last decade, anti-tumour necrosis factor (TNF) agents (such as infliximab and adalimumab) have greatly improved the outcomes of patients with IBD, particularly when administered early in the course of the disease.[1–3] Sustained remission, that is, long-lasting absence of disease activity, has now become a realistic treatment target. Real-world evidence studies have shown that 67%–91% of paediatric patients and up to 66% of adult patients is in sustained remission 2 years after the initiation of anti-TNF therapy.[4–6]

However, long-term exposure to anti-TNF agents is also associated with dose-dependent susceptibility to infections and dermatological adverse effects. Once sustained remission is achieved, many patients therefore ask whether it is feasible to stop or taper anti-TNF therapy. In fact, optimising current treatment strategies is considered one of the gap areas that must be addressed to get closer to precision medicine in IBD care.[7]

Both patients and healthcare professionals often wish to stop or reduce exposure to medication, provided that the benefits outweigh the risks. Key considerations are the risk of disease relapse, and whether retreatment with the same or other drugs is successful if de-escalation fails. Complete withdrawal of anti-TNF therapy may not be realistic, even when the patient with IBD was treated effectively early after the diagnosis.[8] Dosing interval lengthening, on the other hand, may be a feasible alternative for patients in sustained remission who wish to reduce exposure to anti-TNF agents.[9] Preliminary, uncontrolled studies suggest that interval lengthening is feasible in a relevant proportion of patients with IBD, as long as faecal calprotectin (FC) measurements are performed periodically to guide therapeutic decisions and antidrug antibodies are not present.[10 11] Studies in patients with rheumatoid arthritis, an autoimmune disorder that has many parallels with IBD, also demonstrated the feasibility of anti-TNF de-escalation.[12]

Preliminary studies on dosing interval lengthening

In a large cohort of Belgian adult patients with CD (n=898) on adalimumab maintenance therapy, Van Steenbergen *et al* selected 40 patients who had de-escalated from a 2-week to a 3-week adalimumab dosing interval. Compared with controls with an unchanged dosing interval, trough levels in these 40 patients had dropped significantly within 4 months, but this did not lead to clinical or biochemical changes. During a median follow-up of 24 months, 65% of the patients maintained clinical remission. Clinical relapse occurred significantly more frequently in patients with a lengthened interval compared with controls (30% vs 3%, respectively) and required reversal to a 2-week dosing interval.[13] In a French observational study that followed patients with IBD after adalimumab interval lengthening to 40 mg every 3 weeks, 17 of 56 patients (30%) had reverted to the standard 2-week dosing interval because of insufficient clinical, biochemical and/or morphological disease control. This was successful in 16 of these 17 patients (94%). Confirmation of transmural healing (by MRI) or endoscopic remission in the year before interval lengthening decreased the risk of symptomatic flare after de-escalation with a factor five.[14]

A Belgian randomised controlled trial (RCT) evaluated the use of infliximab trough-level measurements to decide on the interval between infusions and demonstrated that a 12-week interval is feasible in a proportion of patients.[15]

Relevance for practice

Usually, de-escalation studies are not a research priority for pharmaceutical companies, and consequently industry-initiated RCTs are unlikely to take place.

If the effect of interval lengthening, as proposed in this study protocol, is non-inferior to standard dosing, we feel that it should be part of optimal IBD care.

Second, this study may provide additional support for the *disease modification* hypothesis, that states that chronicity of inflammation can be reduced with early aggressive therapy (ie, anti-TNF agents).[16–18] Studies in young patients with juvenile idiopathic arthritis, who typically have a short disease history, have shown that anti-TNF therapy early in their disease course can create a window of opportunity to successfully de-escalate.[19] It is therefore essential to include adolescents and young adults in de-escalation studies.

Research in context: FC monitoring

Achieving endoscopic (or mucosal) healing is regarded as the ideal therapeutic target in IBD, because its attainment is associated with favourable long-term outcomes.[20] However, frequent endoscopic inspection to evaluate resolution of inflammation is impractical. Persistent low FC levels correspond well with endoscopic healing, as is shown in several observational paediatric and adult studies, and can therefore serve as a proxy for mucosal healing.[21–25]

In previously asymptomatic patients, increasing concentrations of FC that cross the upper limit of the target range predict clinical relapse in the following 2–3 months.[26] Frequent monitoring of FC levels therefore allows early detection of a disease flare. The discussion about the best FC cut-off point for mucosal healing is ongoing. In this study, we will use 250 µg/g for patients with CD and 150 µg/g for patients with UC, based on its correspondence with endoscopic remission.[27–34]

Study objectives

The aim of this study is to evaluate the effectiveness of interval lengthening versus standard dosing after achieving sustained disease remission in patients with IBD, during 1 year of follow-up.

Secondary objectives include the evaluation of (1) the success rate of reversal to standard dosing after a first out-of-range FC result and (2) the cumulative incidence of anti-TNF associated adverse effects after interval lengthening compared with standard dosing.

METHODS AND ANALYSIS

Study design

We designed a prospective, partially randomised patient preference trial that will run in multiple European

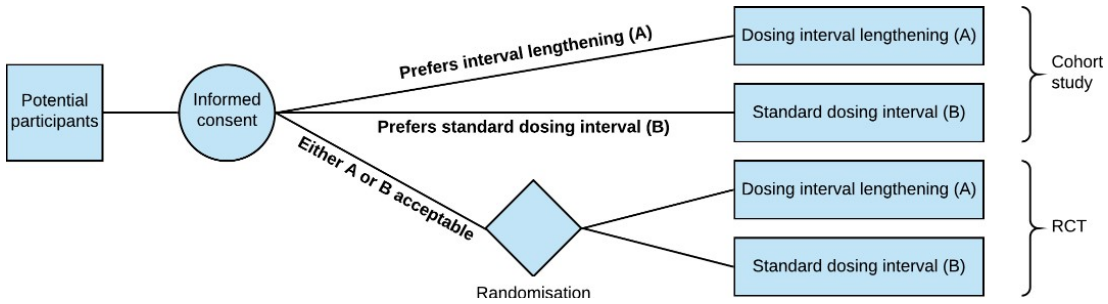

Figure 1 Allocation process. RCT, randomised controlled trial.

centres. Patients will be offered randomisation, but those with strong preferences can choose a strategy instead, and will be followed up identically. Hence, in this trial that compares (A) the lengthened dosing interval with (B) standard dosing interval, we will have four groups: randomised to A; randomised to B; prefer A; prefer B (figure 1). Inclusion of non-randomised patients creates a cohort study alongside an RCT.

The first patient was included on 11 March 2021. Follow-up of the last patient is scheduled to end in the first quarter of 2023.

Inclusion criteria

Eligible patients are 12–25 years old, diagnosed with luminal CD or UC, treated with either 8-weekly infliximab or 2-weekly adalimumab as first ever anti-TNF agent (or as second anti-TNF agent for reasons other than primary non-response or secondary loss of response) and no previous attempts to lengthen the dosing interval. At study entry, patients should be in sustained remission, defined as the absence of symptoms of active IBD, combined with three consecutive FC results in the target range (i.e. <250 µg/g for patients with CD; <150 µg/g for patients with UC) in the previous 6 months, or combined with confirmed endoscopic remission in the last 2 months before study entry (ie, simple endoscopic score for Crohn's disease <3 points; UC endoscopic index of severity ≤1 point or Mayo endoscopic subscore ≤1 point).

Exclusion criteria

Potential participants will be excluded from the study if any of the following conditions occur: perianal fistula, presence of ileostomy or ileoanal pouch (as FC cut-off is not validated for small bowel faeces), any inflammatory comorbidity (such as rheumatoid arthritis), cotreatment with corticosteroids (prednisone or budesonide) or pregnancy.

Intervention group

In patients allocated to the intervention group, the interval between consecutive anti-TNF administrations will be lengthened. The individual dose itself and the choice for either infliximab or adalimumab will remain unaltered. In patients treated with adalimumab, the dosing interval will be lengthened from 2 to 3 weeks. In patients treated with infliximab, the dosing interval will be lengthened from 8 to 12 weeks.

Control group

Patients in the control group will continue on the standard dosing interval of 2 weeks for adalimumab and 8 weeks for infliximab. The dose and choice of anti-TNF agent will remain unaltered.

Use of cointervention

In addition to the anti-TNF agent, stable doses of concomitant maintenance medication will be continued in both groups and include immunomodulators (mercaptopurine, azathioprine, thioguanine or methotrexate) and/or aminosalicylates (sulfasalazine or mesalamine).

During the study period, the use of anti-TNF agents other than infliximab or adalimumab and the use of any investigational drug of chemical or biological nature other than the investigational medicinal products is prohibited, as is participation in other interventional studies.

Primary outcome

The primary outcome is the cumulative incidence of out-of-range FC results at 48-week follow-up. Out-of-range FC results are defined as FC above the target range (i.e. >250 µg/g for patients with CD; >150 µg/g for patients with UC) and at least 100 µg/g increase compared with the previous result, unless the previous result was already above the target range.

Secondary outcomes

Secondary endpoints include (1) time to get out-of-range FC results, defined as the time from study baseline until the first out-of-range FC result as defined above and (2) cumulative incidence of infections and dermatological adverse effects (eg, skin infections, psoriasis, eczema) at 48-week follow-up.[35–37]

Other secondary endpoints are (3) evolution of FC and anti-TNF trough levels in the first 16 weeks after reversal to standard dosing, (4) proportion of patients developing loss of response in the first 16 weeks after reversal to standard dosing, in which loss of response is defined as the appearance of symptoms of active IBD in combination with persistent out-of-range FC results, and (5) identification of predictors of successful de-escalation.

Other outcomes

To obtain insight into the attitude towards deprescribing anti-TNF agents, we will use the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire.

If an out-of-range FC result occurs, faeces of UMCG-based patients will be tested for colon pathogens (*Salmonella enterica*, *Campylobacter jejuni*, *Shigella* spp, *Shiga toxin-producing Escherichia coli*, *Clostridium difficile* and *Cryptosporidium* spp) to control for false-positive FC results.

Sample size

Based on analysis of real-life data in a historical cohort from the coordinating centre (University Medical Centre Groningen, UMCG) the annual baseline risk of out-of-range FC results in young patients with IBD after reaching sustained remission on anti-TNF therapy is 20%.

Interval lengthening is non-inferior to standard dosing if the cumulative incidence of out-of-range FC results (and its 95% CI) is less than +20% different from the control group. This non-inferiority margin corresponds to a 20% increase in out-of-range FC results and should not be confused with a 20% increase in symptomatic flares. We anticipate that <10% of those who develop out-of-range FC results will ultimately progress to secondary loss of response to anti-TNF therapy. We wish to detect this difference by a one-sided test at 2.5% level of significance with a probability of 80%, a non-inferiority margin of 20%, and a 1:1 allocation ratio. With the binary outcome (out-of-range result or not) 64 patients per group will be needed. To accommodate dropouts (5%) and control for potential confounders caused by the inclusion of non-randomised patients (10%), we adjusted the sample size to a total of 74 patients per group.

Allocation

Patients will be recruited from both paediatric and adult IBD clinics from university hospitals in the Netherlands, Spain and Belgium.

As mentioned above, patients will be offered randomisation, but those with strong preferences can choose a strategy instead and will be followed-up identically. In the group of patients that are willing to be randomised, block randomisation with a variable block size (between 4 and 8) stratified for study centre will be performed in a 1:1 ratio. The allocation sequence is generated by the biostatistics unit of the UMCG, and is not available to any member of the research team. Allocation concealment will be ensured, as the REDCap study website will not release the randomization code until the teenager has been recruited into the trial[38 39] The nature of the intervention (lengthening of the dosing interval) does not allow blinding of the different strategies.

Study procedures

Screening

Two weeks prior to baseline, potential participants will be assessed for eligibility. Oral and written information about the study will be provided by the local IBD-team. Patients who do not meet inclusion criteria or who decline to participate, will be recorded anonymously, including patient characteristics and, if available, the reason of non-participation.

Enrolment/baseline assessment

After obtaining written informed consent, each patient will complete the rPATD questionnaire[40–43] and additional questions about anti-TNF de-escalation and a baseline assessment will be performed. FC, anti-TNF trough levels and C reactive protein will be measured (figure 2).

Post-allocation follow-up

Patients will be followed until 48 weeks after study enrolment, or until 16 weeks after the first out-of-range FC. FC will be measured every 4 weeks with a validated point-of-care test[44 45] (IBDoc, Bühlmann Laboratories AG, Schönenbuch, Switzerland) and a software application that turns a personal smartphone camera into a reader for quantitative measurements. At the same time, patients will self-monitor their symptoms of (impending) relapse, including abdominal pain, rectal bleeding, semi-formed or liquid stool consistency, increased defecation frequency, nocturnal defecation, a decline in energy level and a decrease of appetite.[46–49] Patients are instructed to contact their local IBD team if symptoms return between preset face-to-face encounters.

Adverse effects of anti-TNF will be assessed by self-reporting at weeks 12 and 36, and by the physician during face-to-face encounters at weeks 24 and 48. Anti-TNF trough levels will be measured every 12 weeks after interval lengthening and every 24 weeks in the cohort with standard dosing.

As soon as an out-of-range FC result is detected, treatment will be intensified according to protocol. In the intervention group, this primarily consists of reversal to standard anti-TNF dosing. After an out-of-range FC result, patients are followed for another 16 weeks, after which participation to the study is terminated. Follow-up after an out-of-range FC result consists of self-assessment of symptoms of relapse and FC testing every 4 weeks, and a face-to-face evaluation with anti-TNF trough level measurement every 8 weeks.

Adherence and retention

In this study, adherence refers to the degree to which patients act on reminders that it is time to perform a next FC measurement and complete a next online questionnaire. Low adherence can have a substantial effect on the interpretation of the study results. To help avoid these potential detrimental effects of non-adherence, we have implemented the following procedures: (1) reminding patients automatically (by email) to complete a questionnaire and to perform an FC measurement. This reminder is resent every 3 days for up to three times if a participant has not responded. (2) Mentioning the importance of keeping to agreements in the written patient information that patients receive upfront. (3) Emphasising the importance of keeping to agreements during the face-to-face baseline evaluation. (4) If applicable, discussing the

	STUDY PERIOD													
	Enrolment	Allocation	Post-allocation (4-week intervals)											Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}	t_{12}*
ENROLMENT:														
Eligibility screen	X	X												
Informed consent		X												
Allocation		X												
INTERVENTIONS:														
Dosing interval lengthening		→	→	→	→	→	→	→	→	→	→	→	→	
Standard dosing		→	→	→	→	→	→	→	→	→	→	→	→	
ASSESSMENTS:														
Baseline variables		X												
rPATD questionnaire		X												
Symptoms of relapse (y/n)			X	X	X	X	X	X	X	X	X	X	X	X
Adverse effects		X			X			X			X			X
Faecal calprotectin		X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-TNF trough level		X			X†			X			X†			X
DE or IS required (y/n)			X	X	X	X	X	X	X	X	X	X	X	X
Patient refuses further participation (y/n)			X	X	X	X	X	X	X	X	X	X	X	X

Figure 2 Schedule of enrolment, interventions, and assessments. Black arrows=scheduled start of intervention; grey arrows=continuation, unless faecal calprotectin is out of range; DE, dose escalation; IS, interval shortening; rPATD, revised Patients' Attitudes Towards Deprescribing. * or 16 weeks after first out-of-range FC. † only in the intervention group.

reason(s) for non-adherence with the patient, either by phone or during a face-to-face evaluation.

The study sites will make every reasonable effort to follow the participants for the entire study period. If a patient is lost to follow-up or withdraws from the study, data that have already been collected until that point will be used in the analyses. If available, a reason for withdrawal will be recorded.

Confidentiality and data management

Patients will receive a study ID number at enrolment. All data will be entered and stored linked to this study ID number. All study-related information will be securely stored electronically or at the study site. Patient information will be stored in electronic Case Report Forms in REDCap or in locked file cabinets if electronic storage is not possible.

Questionnaires will be completed digitally via a hyperlink sent by the REDCap study website. This will automatically be linked to the patient's study ID number.

Data will be stored during the study period and 25 years thereafter. If patients (and their parents in case of minors) give permission, residual serum will be stored for a maximum of 15 years at the local study site for future research.

Data monitoring

An independent Data Safety Monitoring Board (DSMB) has been established. The DSMB consists of three members: Thalia Hummel, MD PhD (chair, paediatric gastroenterologist at Medical Spectrum Twente, Enschede, The Netherlands), Anke Heida, MD PhD (epidemiologist at UMCG) and Douwe Postmus, PhD (statistician at UMCG). The DSMB charter and responsibilities of the DSMB are available on request.

The DSMB will receive results of an interim analysis in confidentiality when 50% of the participants have completed follow-up. Based on this interim analysis, the DSMB will advise as to whether the detected risk levels are acceptable.

The advice of the DSMB will only be sent to the sponsor. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing Medical Research Ethics Committee (MREC), including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Adverse events

In this study, adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the investigational

product or the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff after enrolment will be recorded. Adverse events that meet the criteria of serious adverse events will be reported to the accredited MREC according to the regulations of the concerned country.

Patient and public involvement

In 2015, the structure of the James Lind Alliance Priority Setting Partnership was used to identify and prioritise unanswered questions about treatments for IBD. This process culminated in a Top 10 of Research priorities. Priority number 1 is about the optimal treatment strategy, selecting the right patient group, the right stage of the disease and assessing the potential for withdrawal.[50 51]

Statistical analysis

Data analysis will be coordinated by a statistician from the biostatics unit of the UMCG. The primary analyses will be conducted according to intention to treat. Secondary analyses will be conducted on a per-protocol base. A priori subgroup analyses will be performed to evaluate the effect of dose interval lengthening in two subtypes of IBD (CD and UC) and for both anti-TNF agents (infliximab and adalimumab). Baseline characteristics and outcomes of the randomised group will be compared with the combined randomised and preference group. Descriptive statistics will be used to compare baseline characteristics per allocated arm. Random missing data will be handled by using the multiple imputation Hot Deck method. The threshold for significance is set at 5% ($p<0.05$).

Differences in cumulative incidence of out-of-range FC results between groups at 48 weeks will be analysed with a logistic regression model. Time-to-out-of-range FC results will be visualised with Kaplan-Meier curves. The HR with its 95% CI for out-of-range FC results will be provided with a Cox proportional hazards (multivariate) regression analysis. Potential confounding factors, including age at diagnosis and relapse-free interval before study enrolment will be included in the Cox proportional hazards model.

Statistical comparisons of the baseline characteristics and other secondary outcome measures will be analysed by means of independent samples t-tests, χ^2 test, or Mann-Whitney tests, where appropriate. Predictors of successful de-escalation will be assessed by calculating ORs with the use of univariate logistic regression analysis. Candidate predictors with $p<0.10$ in univariate analysis will be selected for use in the multivariate analysis. An interim safety analysis will be performed by an independent biostatistician when 50% of patients have completed the study.

DISCUSSION

With this study, we aim to determine whether the interval between consecutive anti-TNF administrations can be prolonged by 50% without compromising disease control in patients with IBD who have reached sustained clinical remission. The level of disease control will be tightly monitored via 4-weekly FC screening: out-of-range calprotectin levels will prompt reversal of the anti-TNF treatment interval to the standard dosing interval.

To date, convincing scientific evidence on the feasibility of anti-TNF interval lengthening is lacking. At the same time, patients often wish to stop or reduce exposure to this medication, in particular when they experience side effects associated with long-term exposure. Bridging this knowledge gap is an important step towards optimised IBD care. Provided that disease control is not jeopardised, interval lengthening of anti-TNF medication reduces the number of hospital visits for infliximab and the number of intravenous or subcutaneous administration of anti-TNF agents. In addition, interval lengthening can be expected to reduce anti-TNF associated side-effects as well as medical expenditure.

This study is designed as a partially randomised patient-preference trial. This design combines the methodology of an RCT and a patient preference clinical trial.[52] Patients will be offered randomisation, but those with strong preferences can choose a strategy instead. Inclusion of non-randomised patients in our study will offer some reassurance that the results can be extrapolated to a wider group of patients.[53] A potential limitation of the partially randomised patient preference design is that it may compromise internal validity. Separate analyses will therefore be performed on the randomised and the preference group.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the study protocol and the principles of the Declaration of Helsinki (version 2013).[54] The study protocol has been approved at the primary site by the Medical Ethics Review Committee of the UMCG (METc 2020/340). At the secondary sites, seeking ethical approval is ongoing. In case of important protocol amendments, the Research Ethics Boards will be informed and the clinical trial registry will be updated. Written informed consent will be obtained from all patients and parents/legal guardians of minor patient prior to enrolment. Patients will be permitted to withdraw from the study at any time.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be approved by the MREC prior to implementation and notified to the participating centres.

Results of the study will be disseminated in peer-reviewed journals and presented at scientific meetings.

Author affiliations
[1]Department of Paediatric Gastroenterology, Hepatology and Nutrition, University Medical Centre Groningen, Beatrix Childrens Hospital, Groningen, The Netherlands
[2]Department of Gastroenterology and Hepatology, University Medical Centre Groningen, Groningen, The Netherlands
[3]Department of Gastroenterology, University Hospital Ghent, Gent, Belgium
[4]Department of Gastroenterology, Central University Hospital of Liege, Liege, Belgium
[5]Department of Paediatric Gastroenterology, University Hospital Ghent, Gent, Belgium
[6]Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands
[7]Department of Gastroenterology, Bellvitge University Hospital, IDIBELL, L'Hospitalet de Llobregat, Spain

Twitter Henk Groen @Groen62H, Jordi Guardiola @JordiGuardiolac and Patrick van Rheenen @PFvRheenen

Contributors GD, TL, JG, EL, SvB and PvR initiated this study. MB and PvR drafted, reviewed and revised the manuscript. GD, TL, JG, EL, SvB and WSL reviewed and revised the manuscript. HG provided statistical expertise in clinical trial design. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Marleen Bouhuys http://orcid.org/0000-0001-6530-2198
Henk Groen http://orcid.org/0000-0002-6629-318X
Patrick van Rheenen http://orcid.org/0000-0003-3867-2665

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