BMJ Open

# Predicting response to iron supplementation in patients with active inflammatory bowel disease (PRIme): a randomised trial protocol

Roberta Loveikyte ,[1,2] Marjolijn Duijvestein,[3] Zlatan Mujagic,[4] Rogier L Goetgebuer,[5] Gerard Dijkstra,[2] Andrea E van der Meulen-de Jong[1]

**To cite:** Loveikyte R, Duijvestein M, Mujagic Z, *et al*. Predicting response to iron supplementation in patients with active inflammatory bowel disease (PRIme): a randomised trial protocol. *BMJ Open* 2024;**14**:e077511. doi:10.1136/bmjopen-2023-077511

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-077511).

Received 07 July 2023
Accepted 15 January 2024



For numbered affiliations see end of article.

**Correspondence to**
Roberta Loveikyte;
r.loveikyte@lumc.nl

## ABSTRACT

**Introduction** Iron deficiency anaemia (IDA) is the most common systemic manifestation of inflammatory bowel disease (IBD) that has detrimental effects on quality of life (QoL) and disease outcomes. Iron deficiency (ID), with or without anaemia, poses a diagnostic and therapeutic challenge in patients with IBD due to the multifactorial nature of ID(A) and its frequent recurrence. Elevated hepcidin—a systemic iron regulator that modulates systemic iron availability and intestinal iron absorption—has been associated with oral iron malabsorption in IBD. Therefore, hepcidin could assist in therapeutic decision-making. In this study, we investigate whether hepcidin can predict response to oral and intravenous iron supplementation in patients with active IBD undergoing anti-inflammatory treatment.

**Methods and analysis** PRIme is an exploratory, multicentre, open-label and randomised trial. All adult patients with active IBD and ID(A) will be assessed for eligibility. The participants (n=90) will be recruited at five academic hospitals within the Netherlands and randomised into three groups (1:1:1): oral ferrous fumarate, oral ferric maltol or intravenous iron. Clinical and biochemical data will be collected at the baseline and after 6, 14 and 24 weeks. Blood samples will be collected to measure hepcidin and other biomarkers related to iron status. In addition, patient-reported outcomes regarding QoL and disease burden will be evaluated. The primary outcome is the utility of hepcidin as a predictive biomarker for response to iron therapy, which will be assessed using receiver operating curve analysis.

**Ethics and dissemination** The study has been approved by the Institutional Review Board at the Leiden University Medical Center (IRB No. P21.109) and other study sites. All participants will provide written informed consent to enrol in the study. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences; the dataset will be available on reasonable request.

**Trial registration** Prospectively registered in the https://clinicaltrials.gov/ and the Eudra registries. First submitted on 10 May 2022 to the ClinicalTrials.gov (ID: NCT05456932) and on 3 March 2022 to the European Union Drug Regulating Authorities Clinical Trials Database (ID: 2022-000894-16).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The PRIme trial is the first prospective and randomised study designed to assess whether hepcidin can predict response to oral ferrous fumarate, oral ferric maltol and intravenous iron therapy in patients with inflammatory bowel disease.
⇒ The study intervention includes three most common iron formulations: enteral ferrous salt, enteral iron bound to a carbohydrate and intravenous iron. This comprehensive approach includes a traditional and a newer type of enteral iron.
⇒ Iron deficiency (ID) and excess can affect the redox status and the intestinal microbiota, but the data are scarce. The PRIme trial addresses changes in oxidative stress and the intestinal microbiota during iron therapy.
⇒ ID will be identified based on routinely used biochemical parameters rather than the gold standard: iron staining in bone marrow aspirate.
⇒ As an explorative study, the PRIme trial has a relatively small sample size, with 90 patients randomised to one of the three iron therapy groups.

## INTRODUCTION

Anaemia is the most common systemic manifestation of inflammatory bowel disease (IBD)—ulcerative colitis (UC) and Crohn's disease (CD)—which are immune-mediated inflammatory conditions marked by a relapsing-remitting inflammation within the gastrointestinal tract.[1 2] Anaemia affects approximately one-fifth of adult outpatients with IBD and up to 74% of hospitalised patients or patients with a recent IBD diagnosis.[3–5] The burden of anaemia is substantial, as it has been associated with a reduced quality of life (QoL), cognitive performance and socioeconomic participation, increased healthcare costs and risk of hospitalisation.[6–9] Anaemia in IBD is often multifactorial, but the most common cause is iron deficiency (ID).[6 10]

Iron is essential for most physiological processes, such as energy metabolism, neurotransmitter synthesis and immune system function. Unsurprisingly, patients with ID or iron deficiency anaemia (IDA) are likely to experience fatigue, depression or anxiety and can present with physical or cognitive impairment.[7 8 11] In 2015, the European Crohn's and Colitis Organisation (ECCO) published guidelines emphasising the need for frequent screening, prompt treatment of anaemia and normalisation of iron stores.[12] According to the guidelines, intravenous iron should be the first-line treatment in patients with active disease or severe anaemia, defined as haemoglobin <6.2 mmol/L (<100 g/L). Given no previous intolerances, oral iron should be prescribed as the first-line treatment for patients with inactive or mildly active IBD.[12]

The safety and efficacy of oral and intravenous iron in patients with IBD have been proven.[13–16] Intravenous iron significantly increases haemoglobin and ferritin over the course of several weeks; however serious adverse events (SAEs) occur in approximately 5% of cases.[17 18] In contrast, oral iron is associated with more frequent gastrointestinal side effects than intravenous iron (OR=3.14, 95% CI 1.34—7.36, p=0.008, $I_2$=0%) and can lead to poor treatment adherence or discontinuation.[18–20] Novel oral iron formulations have been developed to address the challenges posed by the poor tolerability of standard oral iron formulations and high costs of intravenous iron, which often include (multiple) elective admissions for intravenous administration and result in loss of workdays.[17] One of the new oral iron formulations—ferric maltol—has gained attention due to its effectiveness compared with intravenous iron.[21] In addition, newer oral iron formulations, such as ferric maltol or sucrosomial iron, have been postulated to be absorbed differently than standard iron salt compounds and have been associated with excellent therapeutic success likely due to improved enteral absorption that is less affected by hepcidin—a systemic iron regulator that modulates enteral iron absorption and systemic iron availability.[22–26] In contrast to standard iron salt compounds, iron from these newer formulations does not readily dissociate, resulting in lower levels of free luminal iron and, consequently, fewer side effects.[23 24 26] Nevertheless, oral iron therapy in active disease states remains controversial. Murine studies showed that oral iron might exacerbate underlying disease due to excess enteral iron, which alters the intestinal microbiota and increases oxidative stress.[27–29] However, the data are scarce and inconsistent, and these concerns are not limited to oral iron.[30–35] The optimal iron therapy for patients with IBD remains to be determined, as emphasised in a recent Cochrane systematic review.[15]

Oral iron malabsorption in patients with IBD has been associated with elevated hepcidin.[36 37] Hepcidin regulates enteral iron absorption and systemic iron availability by modulating the expression of ferroportin—the only known iron exporter located in enterocytes, macrophages and hepatocytes.[38 39] Inflammation and iron overload increase the expression of hepcidin, causing iron restriction within the iron-storing cells. In contrast, ineffective erythropoiesis, ID and hypoxia reduce hepcidin expression, promoting intestinal iron absorption and effective systemic iron utilisation. Although patients with IBD often suffer from inflammation and ID simultaneously, previous studies have shown that iron status is the primary determinant of hepcidin levels, even in an inflammatory state.[40–44] In addition, hepcidin has been shown to predict (non-)responsiveness to oral or intravenous iron in other patient populations; however, this remains to be determined in patients with IBD.[45 46]

This study aims to evaluate whether hepcidin can predict response to oral and intravenous iron therapy in patients with active IBD undergoing anti-inflammatory treatment. This experimental approach addresses challenges in ID(A) management in patients with active IBD, and it will provide the necessary data for personalised care.

## METHODS

### Study design

PRIme is an exploratory, randomised, open-label, parallel-group, multicentre trial (figure 1) in 90 patients with active IBD and concurrent ID(A). Patients will be randomised (1:1:1) to one of the three treatment groups: oral ferrous fumarate, oral ferric maltol or intravenous iron. The trial protocol is written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines, as noted in the online supplementary table S1: SPIRIT checklist.

### Study aim

The primary aim is to evaluate whether hepcidin levels at baseline can predict response to oral and intravenous iron therapy in patients with active IBD and concurrent ID(A). We hypothesise that patients with low hepcidin levels at baseline will have an adequate response to oral and intravenous iron at week 14, whereas patients with high hepcidin levels at baseline might exhibit a suboptimal response to oral or even intravenous iron.

### Sample size calculation

Sample size calculation is based on the main analysis: calculating three areas under the curve (AUCs), one per treatment group and testing if they are significantly larger than AUC 0.5. To establish that an $AUC_{(hepcidin)}$=0.74 is significantly larger than 0.5 with 80% power at a 0.02 significance level, we will include 30 patients in each treatment group. The sample size accounts for 10% attrition rate and includes Bonferroni correction for multiple testing.

### Recruitment

On obtaining informed consent, the eligibility of the patients will be assessed and patients will be randomised

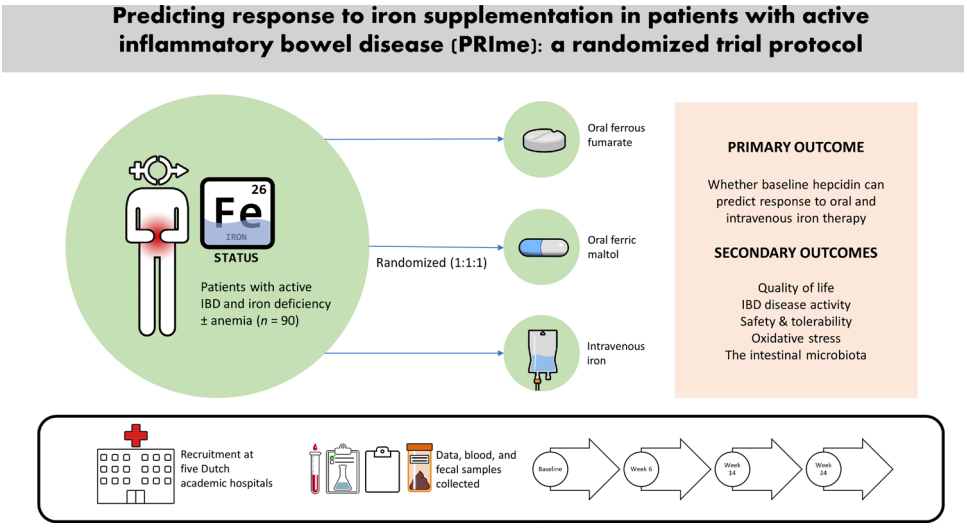


**Figure 1** Graphical abstract.

to one of the three treatment arms. Table 1 represents the trial schedule: enrolment, allocation and study assessments. After the baseline measurements, patients will receive iron therapy. Three follow-up visits are scheduled at weeks 6, 14 and 24 (figure 2). The visit at week 14 marks the end of the treatment, and in cases of inadequate response, patients may receive further iron therapy as part of regular care. The week 24 visit is a 3-month follow-up to evaluate ID(A) recurrence or ID(A) resolution in cases of insufficient response at week 14.

## Participants

Patients with established and active IBD with ID or IDA, who are under treatment at the Department of Gastroenterology and Hepatology in one of the study sites, will be

**Table 1** The PRIme trial: enrolment, intervention and assessments

| | Study period | | | | | |
|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Postallocation | | | Close-out |
| Timepoint | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ | *Same as* $t_3$ |
| ENROLMENT: | | | | | | |
| Eligibility screen | X | | | | | |
| Informed consent | X | | | | | |
| Allocation | | X | | | | |
| INTERVENTIONS: | | | | | | |
| Ferrous fumarate | | ⟷ | ⟷ | ⟷ | | |
| Ferric maltol | | ⟷ | ⟷ | ⟷ | | |
| Intravenous iron | | X | | | | |
| ASSESSMENTS: | | | | | | |
| Demographic data | X | | | | | |
| Anthropometric data | X | | | | X | X |
| Medical history | X | | X | X | X | X |
| IBD classification | X | | | | X | X |
| Medication list | X | | X | X | X | X |
| Laboratory assessments | X | | X | X | X | X |
| Blood samples | X | | X | X | X | X |
| Faecal samples | X | | | X | X | X |
| Patient-reported outcomes | X | | | X | X | X |

IBD, Inflammatory bowel disease.

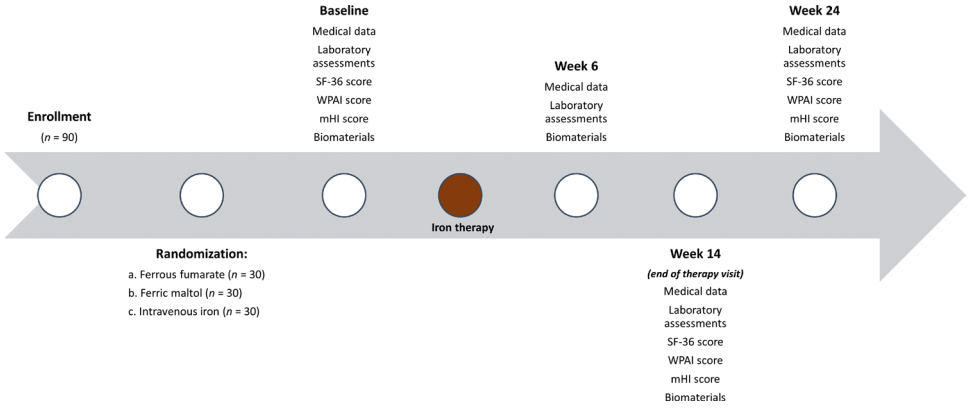


**Figure 2** The PRIme trial. mHI, mobile Health Index questionnaire for assessing clinical inflammatory bowel disease activity and burden; SF-36, Short Form 36 questionnaire for evaluating quality of life; WPAI, Work Productivity and Activity Impairment questionnaire. Biomaterials such as blood and faecal samples will be collected to measure faecal calprotectin, hepcidin and other biomarkers.

considered for enrolment in the study. All study sites are academic hospitals located in the Netherlands, as listed in the ClinicalTrial.gov registry: NCT05456932.

Potential participants will be identified during regular follow-up appointments. Extensive information about the trial will be provided by the treating physician, the principal investigator (PI) or a member of his team, for example, the study coordinator. Up to a week later, potential participants will be contacted again and will have the opportunity to ask questions and consent or decline to participate in the trial. Informed consent will be signed during a planned screening visit. During the trial period, the study coordinator will be available for questions by phone or email to all physicians and study participants at the study sites.

## Inclusion criteria

A patient must meet all of the following criteria in order to be eligible for participation in the study:

1. Established IBD diagnosis (CD, UC or IBD-unclassified).
2. Adults (≥18 years of age)
3. Active IBD based on any radiological or endoscopic activity, or biochemical activity defined as elevated C-reactive protein (CRP; >5 mg/L) or faecal calprotectin (FCP; >150 mg/kg). Routine anti-inflammatory treatment for active IBD must be continued during the study.
4. IDA (defined as ferritin <100 µg/L and haemoglobin <7.5 mmol/L (<120.9 g/L) for females or <8.5 mmol/L (<137 g/L) for males) or ID (defined as ferritin <100 µg/L and transferrin saturation <20% in females and males).

## Exclusion criteria

A patient who meets any of the following criteria will be excluded from participating in the study:

1. Blood transfusion or iron therapy within the past 8 weeks
2. Documented intolerance to oral or intravenous iron
3. Severe anaemia (defined as haemoglobin <6.2 mmol/L (<100 g/L) for females and males)
4. Documented history of liver cirrhosis, heart failure, haemoglobinopathies, autoimmune haemolytic anaemia, myelodysplastic syndrome or chronic obstructive pulmonary disease
5. Documented history of recent treatment for a malignancy (excluding cutaneous basal or squamous cell carcinoma). Patients can be included if the treatment has been finalised ≥6 months prior to enrolment
6. Documented history of gastric or duodenal resections due to benign or malignant pathologies, or bariatric surgery
7. Impaired renal function (defined as estimated glomerular filtration rate <30 mL/min/1.73 $m^2$)
8. Macrocytic anaemia (low haemoglobin along with mean corpuscular volume >100 fL) in combination with folate or vitamin B12 deficiency
9. Pregnancy or breastfeeding at the time of enrolment
10. Major operation (eg, laparotomy) less than 6 weeks prior to enrolment
11. Inability to provide informed consent either due to incapacitation (eg, resulting from cognitive or psychological conditions or hospitalisation in intensive care unit) or inability to understand the Dutch language

## Withdrawal from the study and replacement

Participants have the right to withdraw from the study at any time or for any reason without any consequences. The investigator may also withdraw a participant from the study for medical reasons. In cases of withdrawal due to an adverse event (AE), the event will be registered as the reason for withdrawal. In addition, participants will be withdrawn from the study if they must undergo major surgery or receive a blood transfusion.

## Treatment groups and randomisation

Participants will be randomised using Castor Electronic Data Capture (CastorEDC) block randomisation services. The coordinating investigator will initiate the automatic randomisation sequence, and the results will automatically be registered in the electronic case report form

(eCRF). The coordinating investigator will inform the patient and the treating physician. The investigators have no influence on the automatic randomisation sequence, and the used variable block sizes (ie, sizes 3 and 6) ensure that the investigators cannot predict the outcome. In addition, randomisation will be stratified by disease activity (moderate disease activity defined as either CRP <20 mg/L or FCP <300 mg/kg, and severe disease activity defined as either CRP >20 mg/L or FCP >300 mg/kg).

### Iron therapy with oral ferrous fumarate

Patients randomised to this group will receive iron therapy as an iron salt: 100 mg two times per day ferrous fumarate for 12 weeks. The daily dose corresponds to 65 mg of elemental iron, which is in accordance with the recommended guidelines for patients with IBD.[12] In cases of ferrous fumarate-related AEs (ie, constipation), patients will be advised to consume more fibre or receive stool softeners, such as psyllium fibre. Ferrous fumarate can be used during pregnancy; however, all women of childbearing potential will be counselled to use contraceptive measures since becoming pregnant during periods of active IBD is associated with worse maternal and foetal outcomes.[47]

### Iron therapy with oral ferric maltol

Patients randomised to this group will receive iron therapy in the form of iron bound to polymaltose: 30 mg two times per day ferric maltol for 12 weeks. The daily dose corresponds to 60 mg of elemental iron, which is in accordance with the recommended guidelines for patients with IBD.[12] In cases of ferric maltol-related AEs (ie, constipation), patients will be advised to consume more fibre or receive stool softeners, such as psyllium fibre. Ferric maltol can be used during pregnancy; however, all women of childbearing potential will be counselled to use contraceptive measures since becoming pregnant during periods of active IBD is associated with worse maternal and fetal outcomes.[47]

### Iron therapy with intravenous iron

Patients randomised to this group will receive intravenous iron therapy in one of the formulations used at the participating study sites, that is, ferriderisomaltose or ferric carboxymaltose. The iron dose will be calculated based on the patient's weight and haemoglobin level: 1000 mg for patients weighing up to 70 kg and haemoglobin >6.2 mmol/L; 1500 mg for patients weighing more than 70 kg and haemoglobin >6.2 mmol/L.[12] In cases of intravenous iron-related AEs (eg, urticaria, anaphylaxis), the infusion will be stopped, and patients will be treated as medically indicated. In cases of AEs related to infusion reactions rather than allergic reactions, the intravenous iron infusion will be resumed at a slower infusion rate. Intravenous iron can be used in second and third trimesters, but data for first trimester are lacking. All women of childbearing potential will be counselled to use contraceptive measures since becoming pregnant during periods of active IBD is associated with worse maternal and fetal outcomes.[47]

### Concomitant care

During the study, all patients must continue with anti-inflammatory treatment for active IBD as part of routine care; the type and dosage of the therapy are in the discretion of the treating physician. All changes in IBD therapy will be registered. In addition, iron supplementation outside the study intervention is not allowed during the study period. Other concomitant medication, except for proton pump inhibitors (PPIs) in patients treated with oral iron, may be given as medically indicated. Low pH is necessary for enteral iron to be efficiently absorbed; hence, patients randomised to oral iron groups will be advised to stop taking PPIs or switch to other antacids temporarily. Lastly, patients are not allowed to participate in other intervention trials during the PRIme trial.

### Drug accountability

Study medication will be labelled, stored and disposed of according to the Good Clinical Practice regulation and national laws. Drug accountability will be performed by the investigators using a drug accountability log. Patients will receive regular questionnaires to evaluate their compliance, which will also act as a reminder to stay compliant.

### Patient and public involvement

The PRIme study was initiated by the Leiden University Medical Center (LUMC) in collaboration with other academic centres within the Initiative on Crohn and Colitis (the ICC) network. The design of the study has not been discussed with patient cohorts or communities; however, the ICC and the researchers work closely with the Dutch IBD patient association Crohn & Colitis NL and the Maag Lever Darm Stichting, a non-profit organisation, who have previously indicated the relevance and importance of scientific advancement and the understanding of ID and its treatment in patients with IBD.

## OUTCOMES

### Primary outcome

Baseline hepcidin levels and a binary response to iron therapy will be used to evaluate whether baseline hepcidin levels can predict response to iron therapy (ie, (a) oral ferrous fumarate, (b) oral ferric maltol and (c) intravenous iron). The response to iron therapy is defined as an increase >1.2 mmol/L in haemoglobin or haemoglobin normalisation at week 14 for patients with IDA; or normalisation of iron stores (defined as ferritin >100 µg/L and transferrin saturation >20%) at week 14 for patients with ID.

### Secondary outcomes

1. To assess changes in hepcidin levels from baseline to weeks 6, 14 and 24 in the three groups.

2. To assess changes in inflammation-associated and hypoxia-associated cytokine levels from baseline to weeks 6, 14 and 24 in the three groups.
3. To assess the proportion of patients who achieve normalisation of iron stores at weeks 6, 14 and 24 in the three groups.
4. To assess the relationship between disease activity and response to iron therapy in the three groups.
5. To assess the proportion of patients who experienced hypophosphatemia throughout iron therapy in the three groups.
6. To assess the number of (S)AEs and adverse reactions in the three groups.
7. To assess changes in patient-reported outcomes (ie, Short Form 36, Work Productivity and Activity Impairment (WPAI) Questionnaire and mobile Health Index (mHI) questionnaires[48–50]) from baseline to weeks 14 and 24 in the three groups.
8. To assess the proportion of patients who achieved adequate haematological response or haemoglobin normalisation at weeks 14 and 24 in the three groups.
9. To assess the proportion of patients who experienced ≥0.6 mmol/L change in haemoglobin from baseline to weeks 6 and 14 in the three groups.

### Exploratory outcomes

1. To assess whether hepcidin level at baseline is a universally applicable predictor for iron therapy response (ie, to assess if there is a difference in the predictive capacity between the study groups)
2. To assess changes in microbiota from baseline to weeks 14 and 24
3. To assess changes in oxidative stress from baseline to weeks 6 and 14
4. To assess whether inflammation-associated or hypoxia-associated cytokines can predict hepcidin levels
5. To assess whether other iron-status-related biomarkers, such as soluble transferrin receptor, are better markers for ID compared with ferritin

### Data collection and management

All study data will be recorded in an eCRF using CastorEDC services. Each study participant will be assigned a unique trial pseudonym, ensuring that only pseudonymised data are collected. Following national law, the coordinating centre will only have access to pseudonymised data. Source data, such as medical data from medical records, will be entered into the eCRF by site personnel or the coordinating investigator. The investigator or appropriate designee will sign and validate all data within the eCRF. Collected biomaterials will be processed and stored in a −80°C freezer until analysis.

### AEs and safety

Any undesirable experience occurring to a subject during the study is considered an AE, despite its relation to the study intervention. All AEs reported spontaneously by the subject or observed by the investigator will be recorded in the eCRF. Throughout the study, any event that results in death, is life-threatening (at the time of the event), requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital abnormality, or requires medical or surgical intervention to prevent any other significant medical events will be considered an SAE. Participating sites must report all (S)AEs to the coordinating investigator or the PI. Life-threatening events or death will be reported to the Institutional Review Board within 7 days. All other SAEs will be reported within 15 days using the national registration system (https://www.toetsingonline.nl).

## ANALYSIS

### Statistical analysis

Descriptive analysis will be performed for all baseline and demographic data; continuous variables will be presented as means±SD or medians±IQRs based on the distribution, whereas categorical variables will be presented as proportions of absolute numbers (*n*) with corresponding percentages (%).

Receiver operating characteristics curve with associated AUC will be used to assess the discriminative ability of hepcidin levels at baseline to predict treatment response to iron therapy; these analyses will be performed separately in each of the three treatment groups by computing AUCs with their 95% CIs.

We will perform univariable analyses to study the relationships between outcome variables and covariables. We will base our analyses on the type and distribution of the variables and use (un)paired t-test, Wilcoxon rank-sum test, (paired) ANOVA, Kruskal-Wallis test, Mann-Whitney U test, McNemar's test, and Pearson or Spearman's correlations. In addition, we will perform univariable and multivariable linear (mixed-effects) regression analysis to investigate the association between the treatment changes in hepcidin, hypoxia-associated or inflammation-associated cytokines, as well as changes in QoL, WPAI and mHI. We will adjust our regression analyses for potential confounders, which we will describe in the final manuscript.

If necessary, missing data will be handled using imputation and described in the final manuscript. A two-sided $p<0.05$ will be considered statistically significant. Where applicable, we will adjust our analyses for multiple testing using the Benjamini-Hochberg procedure adopting a 5% false discovery rate. All analyses will be performed using the SPSS Statistics 29 software package (IBM).

### Study coordination and monitoring

PRIme is coordinated by the primary project leader and the coordinating investigator, who are employed at the LUMC. The primary project leader and coordinating investigator have weekly meetings to discuss the progress. Principal and local investigators are responsible for the day-to-day trial support at the study sites. The coordinating

investigator is the primary point of contact for study sites and will be responsible for data analysis.

The LUMC will assign a trial monitor. According to the monitoring plan, the monitor will assess the progress of the trial, study documentation, (S)AE reporting and study data. Monitoring frequency will be decided based on the monitor's findings after every visit. In addition, annual progress and safety reports will be submitted to the Institutional Review Board, which can decide whether to continue, modify or terminate the trial based on the reports.

### Amendments

All amendments, except for minor changes in logistics or administration, will be submitted to the Institutional Review Board at the LUMC. All significant amendments impacting participants will be communicated to the study participants.

### Ethics and dissemination

The study has been approved by the Institutional Review Board at the LUMC (IRB No. P21.109) and other study sites. The final study manuscript will be published in a peer-reviewed journal. The study results will be communicated to medical professionals through a peer-reviewed publication and conference presentations; local newsletters will be used to share the results with the patient population.

## DISCUSSION

The high prevalence of ID(A) and its frequent recurrence, combined with a lack of evidence regarding the most effective iron therapy in patients with IBD, highlights the need to address this therapeutic issue.[3 15] Despite the ECCO guidelines emphasising the importance of prompt iron repletion, studies have shown that ID(A) is often left untreated.[3 5 51 52] In addition, studies have observed a preference for one or the other iron modality; we have shown that intravenous iron is prescribed in over 50% of cases regardless of disease activity.[3 5 53] In the Netherlands, the *standard practice* to prescribe intravenous iron to patients irrespective of complaints, the severity of ID(A) or IBD activity has created the notion that oral iron formulations are ineffective. Consequently, we encounter physicians and patients who strongly prefer intravenous iron based on habit rather than well-established allergies or intolerances to oral iron. We believe that personalised iron therapy, guided by hepcidin levels, can provide valuable information for targeted and effective iron therapy, as well as address the current biases formed by patients and physicians alike.

Untargeted or inappropriate iron supplementation in patients with IBD could lead to iron excess, oxidative stress and deleterious alterations in the intestinal microbiota.[33–35] Anti-inflammatory therapy reduces hepcidin levels in different patient populations, which might lead to better bioavailability of iron supplements.[40 54] Given that patients with IBD often suffer from ID and inflammation simultaneously, it is imperative to establish hepcidin levels to prevent inappropriate iron supplementation. In addition, tailoring iron therapy based on hepcidin levels could mitigate potential side effects and reduce healthcare-associated costs, for example, prescribing oral rather than intravenous iron for patients with low hepcidin would prevent unnecessary admission and loss of workdays; in contrast, avoiding oral iron therapy in patients with elevated hepcidin would prevent clinical complaints associated with excess intestinal iron. In short, hepcidin-guided iron therapy could prevent adverse effects commonly associated with iron supplementation.

To our knowledge, this is the first trial investigating response prediction to different forms of iron therapy in patients with active IBD, especially in a prospective and randomised setting. However, the study also has limitations. In the PRIme trial, we will include patients with active IBD who are undergoing anti-inflammatory treatment as part of routine care. Different anti-inflammatory therapies may have varying effects on inflammatory cytokines and hepcidin levels, potentially influencing the response to iron therapy throughout the study. Furthermore, there is no universal cut-off point for ferritin to diagnose ID in healthy volunteers or patients with IBD. In the PRIme trial, ferritin <100 µg/L will be used to establish ID during active IBD, based on the ECCO consensus guidelines.[12] To address these limitations to the best of our ability, we will conduct analyses based on disease activity and other iron parameters, such as soluble transferrin receptor. Despite these limitations, the PRIme trial will provide the necessary data for personalised iron therapy aimed at preventing frequent ID(A) recurrence, potential adverse effects and associated decline in QoL.

### Trial status

The trial was registered in the ClinicalTrials.gov registry (NCT05456932). The first patient was randomised on 8 June 2022. The trial is ongoing and actively recruiting. To date, 26 patients have been randomised, but 6 have been excluded or lost to follow-up. The recruitment will be continued until 2026; the period will be extended if necessary.

**Author affiliations**
[1]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands
[3]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands
[4]Department of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands
[5]Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands

**Acknowledgements** The authors would like to thank the other members of the clinical and trial team for fruitful collaboration. The authors would especially like to thank all the patients participating in the study.

**Contributors** AEvdMJ and GD are the principal investigators. Together with RL, they conceived the study, developed the protocol, and acquired funding. AEvdMJ, GD, MD, ZM and RLG are responsible for patient recruitment, data and biomaterial acquisition. Under the supervision of AEvdMJ and GD, RL drafted the initial manuscript. RL made the figures and tables. AEvdMJ, GD, MD, ZM, RLG and RL have read the first draft, provided comments, revised drafts and approved the final manuscript. GD and AEvdMJ are joint last authors.

**Funding** This is an investigator-initiated study and has been partially funded by Norgine Ltd. In addition, Norgine Ltd. has provided ferric maltol for this study at no cost.

**Competing interests** GD has received research grants from the Royal DSM, and speaker's fees from Janssen Pharmaceuticals, Takeda, Pfizer and AbbVie. AEvdMJ has received unrestricted research grants from Galapagos, Norgine Ltd., Vedanta, Ferring, and Nestle, and speaker's fees from Galapagos, Tramedico, Takeda, and Janssen Pharmaceuticals. RL has received advisory fees from Cablon Medical and received travel fees from Galapagos and Cablon Medical. ZM has received unrestricted grants from Niels Stensen Fellowship, MLDS, and Galapagos. MD received advisory fees from Echo Pharma and Robarts Clinical Trials, Inc., and speaker's fees from Janssen Pharmaceuticals, Merck & Co., Inc., Pfizer, Takeda, and Tillotts Pharma, as well as non-financial support from Dr Falk.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iD**

Roberta Loveikyte http://orcid.org/0000-0002-3183-9007

## REFERENCES

1 van den Heuvel TRA, Jeuring SFG, Zeegers MP, *et al*. A 20-year temporal change analysis in incidence, presenting phenotype and mortality, in the Dutch IBDSL cohort-can diagnostic factors explain the increase in IBD incidence? *J Crohns Colitis* 2017;11:1169–79.
2 Van Linschoten R, van Leeuwen N, Hazelzet JA, *et al*. OP25 prevalence of IBD in the Netherlands: development and validation of machine learning models for administrative data. *J Crohns Colitis* 2023;17:i34–5.
3 Loveikyte R, Boer M, van der Meulen CN, *et al*. Anemia and iron deficiency in outpatients with inflammatory bowel disease: ubiquitous yet suboptimally managed. *J Clin Med* 2022;11:6843.
4 Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med* 2004;116 Suppl 7A:44S–49S.
5 Peyrin-Biroulet L, Bouguen G, Laharie D, *et al*. Iron deficiency in patients with inflammatory bowel diseases: a prospective multicenter cross-sectional study. *Dig Dis Sci* 2022;67:5637–46.
6 Bergamaschi G, Castiglione F, D'Incà R, *et al*. Prevalence, pathogenesis and management of anemia in inflammatory bowel disease: an IG-IBD multicenter, prospective, and observational study. *Inflamm Bowel Dis* 2023;29:76–84.
7 Gasche C, Lomer MCE, Cavill I, *et al*. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004;53:1190–7.
8 Dugan C, MacLean B, Cabolis K, *et al*. The misogyny of iron deficiency. *Anaesthesia* 2021;76 Suppl 4:56–62.
9 Blaney H, Vu P, Mathew A, *et al*. Anemia severity associated with increased healthcare utilization and costs in inflammatory bowel disease. *Dig Dis Sci* 2021;66:2555–63.
10 Filmann N, Rey J, Schneeweiss S, *et al*. Prevalence of anemia in inflammatory bowel diseases in european countries: a systematic review and individual patient data meta-analysis. *Inflamm Bowel Dis* 2014;20:936–45.
11 König P, Jimenez K, Saletu-Zyhlarz G, *et al*. Iron deficiency, depression, and fatigue in inflammatory bowel diseases. *Z Gastroenterol* 2020;58:1191–200.
12 Dignass AU, Gasche C, Bettenworth D, *et al*. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015;9:211–22.
13 Abhyankar A, Moss AC. Iron replacement in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;21:1976–81.
14 Nielsen OH, Ainsworth M, Coskun M, *et al*. Management of iron-deficiency anemia in inflammatory bowel disease: a systematic review. *Medicine (Baltimore)* 2015;94:e963.
15 Gordon M, Sinopoulou V, Iheozor-Ejiofor Z, *et al*. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. *Cochrane Database Syst Rev* 2021;1:CD013529.
16 Bevers N, Van de Vijver E, Aliu A, *et al*. Ferric carboxymaltose versus ferrous fumarate in anemic children with inflammatory bowel disease: the POPEYE randomized controlled clinical trial. *J Pediatr* 2023;256:113–9.
17 D'Amico F, Peyrin-Biroulet L, Danese S. Oral iron for IBD patients: lessons learned at time of COVID-19 pandemic. *J Clin Med* 2020;9:1536.
18 Bonovas S, Fiorino G, Allocca M, *et al*. Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016;95:e2308.
19 Tolkien Z, Stecher L, Mander AP, *et al*. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One* 2015;10:e0117383.
20 Gómez-Ramírez S, Brilli E, Tarantino G, *et al*. Sucrosomial® iron: a new generation iron for improving oral supplementation. *Pharmaceuticals (Basel)* 2018;11:97.
21 Howaldt S, Domènech E, Martinez N, *et al*. Long-term effectiveness of oral ferric maltol vs intravenous ferric carboxymaltose for the treatment of iron-deficiency anemia in patients with inflammatory bowel disease: a randomized controlled noninferiority trial. *Inflamm Bowel Dis* 2022;28:373–84.
22 Kontoghiorghes GJ, Kolnagou A, Demetriou T, *et al*. New era in the treatment of iron deficiency anaemia using trimaltol iron and other lipophilic iron chelator complexes: historical perspectives of discovery and future applications. *Int J Mol Sci* 2021;22:5546.
23 Gómez-Ramírez S, Brilli E, Tarantino G, *et al*. Sucrosomial® iron: an updated review of its clinical efficacy for the treatment of iron deficiency. *Pharmaceuticals (Basel)* 2023;16:847.
24 Schmidt C, Allen S, Kopyt N, *et al*. Iron replacement therapy with oral ferric maltol: review of the evidence and expert opinion. *J Clin Med* 2021;10:4448.
25 Quraishi N, Smith S, Ward D, *et al*. Disease activity affects response to enteral iron supplementation; post-hoc analysis of data from the aegis study. *Gut* 2017;66:A262.
26 Kumar A, Sharma E, Marley A, *et al*. Iron deficiency anaemia: pathophysiology, assessment, practical management. *BMJ Open Gastroenterol* 2022;9:e000759.
27 Mahalhal A, Burkitt MD, Duckworth CA, *et al*. Long-term iron deficiency and dietary iron excess exacerbate acute dextran sodium sulphate-induced colitis and are associated with significant dysbiosis. *Int J Mol Sci* 2021;22:3646.
28 Mahalhal A, Williams JM, Johnson S, *et al*. Oral iron exacerbates colitis and influences the intestinal microbiome. *PLoS One* 2018;13:e0202460.
29 Mahalhal A, Frau A, Burkitt MD, *et al*. Oral ferric maltol does not adversely affect the intestinal microbiome of patients or mice, but ferrous sulphate does. *Nutrients* 2021;13:2269.
30 Rizvi S, Schoen RE. Supplementation with oral vs. intravenous iron for anemia with IBD or gastrointestinal bleeding: is oral iron getting a bad rap? *Am J Gastroenterol* 2011;106:1872–9.
31 Lee T, Clavel T, Smirnov K, *et al*. Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut* 2017;66:863–71.
32 La Carpia F, Wojczyk BS, Annavajhala MK, *et al*. Transfusional iron overload and intravenous iron infusions modify the mouse gut microbiota similarly to dietary iron. *NPJ Biofilms Microbiomes* 2019;5:26.

33 Puga AM, Samaniego-Vaesken M de L, Montero-Bravo A, *et al*. Iron Supplementation at the Crossroads of Nutrition and Gut Microbiota: The State of the Art. *Nutrients* 2022;14:1926.
34 Malesza IJ, Bartkowiak-Wieczorek J, Winkler-Galicki J, *et al*. The dark side of iron: the relationship between iron, inflammation and gut microbiota in selected diseases associated with iron deficiency anaemia-a narrative review. *Nutrients* 2022;14:3478.
35 Loveikyte R, Bourgonje AR, van Goor H, *et al*. The effect of iron therapy on oxidative stress and intestinal microbiota in inflammatory bowel diseases: a review on the conundrum. *Redox Biol* 2023;68:102950.
36 Martinelli M, Strisciuglio C, Alessandrella A, *et al*. Serum hepcidin and iron absorption in pediatric inflammatory bowel disease: a prospective, comparative study. *Digestive and Liver Disease* 2014;46:e92.
37 Aksan A, Wohlrath M, Iqbal TH, *et al*. Inflammation, but not the underlying disease or its location, predicts oral iron absorption capacity in patients with inflammatory bowel disease. *J Crohns Colitis* 2020;14:316–22.
38 Rishi G, Subramaniam VN. Signaling pathways regulating hepcidin. *Vitam Horm* 2019;110:47–70.
39 Roth MP, Meynard D, Coppin H. Regulators of hepcidin expression. *Vitam Horm* 2019;110:101–29.
40 Loveikyte R, Bourgonje AR, van der Reijden JJ, *et al*. Hepcidin and iron status in patients with inflammatory bowel disease undergoing induction therapy with vedolizumab or infliximab. *Inflamm Bowel Dis* 2023;29:1272–84.
41 Stoffel NU, Lazrak M, Bellitir S, *et al*. The opposing effects of acute inflammation and iron deficiency anemia on serum hepcidin and iron absorption in young women. *Haematologica* 2019;104:1143–9.
42 Darshan D, Frazer DM, Wilkins SJ, *et al*. Severe iron deficiency blunts the response of the iron regulatory gene Hamp and pro-inflammatory cytokines to lipopolysaccharide. *Haematologica* 2010;95:1660–7.
43 Theurl I, Schroll A, Nairz M, *et al*. Pathways for the regulation of hepcidin expression in anemia of chronic disease and iron deficiency anemia in vivo. *Haematologica* 2011;96:1761–9.
44 Mecklenburg I, Reznik D, Fasler-Kan E, *et al*. Serum hepcidin concentrations correlate with ferritin in patients with inflammatory bowel disease. *J Crohns Colitis* 2014;8:1392–7.
45 Bregman DB, Morris D, Koch TA, *et al*. Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol* 2013;88:97–101.
46 Litton E, Baker S, Erber W, *et al*. Hepcidin predicts response to IV iron therapy in patients admitted to the intensive care unit: a nested cohort study. *J Intensive Care* 2018;6:60.
47 Bröms G. IBD in the postpartum period: spotlight on maternal outcomes. *Inflamm Bowel Dis* 2022;28:980–1.
48 Van Deen WK, van der Meulen-de Jong AE, Parekh NK, *et al*. Development and validation of an inflammatory bowel diseases monitoring index for use with mobile health technologies. *Clin Gastroenterol Hepatol* 2016;14:1742–50.
49 Reilly MC, Gerlier L, Brabant Y, *et al*. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. *Clin Ther* 2008;30:393–404.
50 McHorney CA, Ware JE Jr, Lu JF, *et al*. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994;32:40–66.
51 Bengi G, Keyvan H, Durmaz SB, *et al*. Frequency, types, and treatment of anemia in Turkish patients with inflammatory bowel disease. *World J Gastroenterol* 2018;24:4186–96.
52 Lupu A, Diculescu M, Diaconescu R, *et al*. Prevalence of anemia and iron deficiency in Romanian patients with inflammatory bowel disease: a prospective multicenter study. *J Gastrointestin Liver Dis* 2015;24:15–20.
53 Khan N, Patel M, Sundararajan R. P352 Occurrence of moderate to severe anaemia and utilization and efficacy of intravenous iron therapies in a nationwide cohort of Inflammatory Bowel Disease patients. *J Crohns Colitis* 2023;17:i489.
54 Song S-NJ, Iwahashi M, Tomosugi N, *et al*. Comparative evaluation of the effects of treatment with tocilizumab and TNF-α inhibitors on serum hepcidin, anemia response and disease activity in rheumatoid arthritis patients. *Arthritis Res Ther* 2013;15:R141.


**Supplementary Table S1: SPIRIT checklist**.

| 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 | Pages 1–2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Pages 1–2, 6, 16 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Page 1 (exception: the dataset will not be made publicly available, but it will be available on reasonable request) |
| Protocol version | 3 | Date and version identifier | Page 1 |
| Funding | 4 | Sources and types of financial, material, and other support | Pages 1, 16 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Pages 1, 16 |
| | 5b | Name and contact information for the trial sponsor | Cover page, page 1 |
| | 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 | Pages 1, 16 |
| | 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) | Page 14 |

**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 | Pages 4–5 |
| | 6b | Explanation for choice of comparators | Pages 4–5, 9 |
| Objectives | 7 | Specific objectives or hypotheses | Pages 6, 11 |
| 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) | Pages 6–10 |

**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 | Page 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Pages 7–8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Pages 8–10 |
| | 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) | Pages 8–10 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 7–12 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Pages 10 |
| 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 | Pages 11–12 |
| 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 | Figure 2, Table 1; pages 6–10 |

| | | | |
|---|---|---|---|
| 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 | Page 6 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Pages 6–7 |
| **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 | Page 8 |
| 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 | Pages 6–8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions | Pages 6–8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Pages 6–8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | Not applicable |
| **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 | Pages 6–14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Pages 6–14 |

| | | | |
|---|---|---|---|
| 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 | Pages 12–14 |
| 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 | Page 13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | Page 13 |
| **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 | Pages 12–14 |
| | 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 | Not applicable. No interim analyses. |
| 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 | Page 12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Page 14 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Pages 14, 17 |
| 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) | Page 14 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32) | Pages 6–7 |

| | | | |
|---|---|---|---|
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Not 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 | Page 12 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 17 |
| 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 | Pages 12, 17 |
| 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 | Page 16 |
| 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 | Pages 16–17 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Not applicable |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Page 17 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorized surrogates | Consent form is written in the Dutch language and is provided as Supplemental Material. |
| 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 | Page 12 |