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

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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

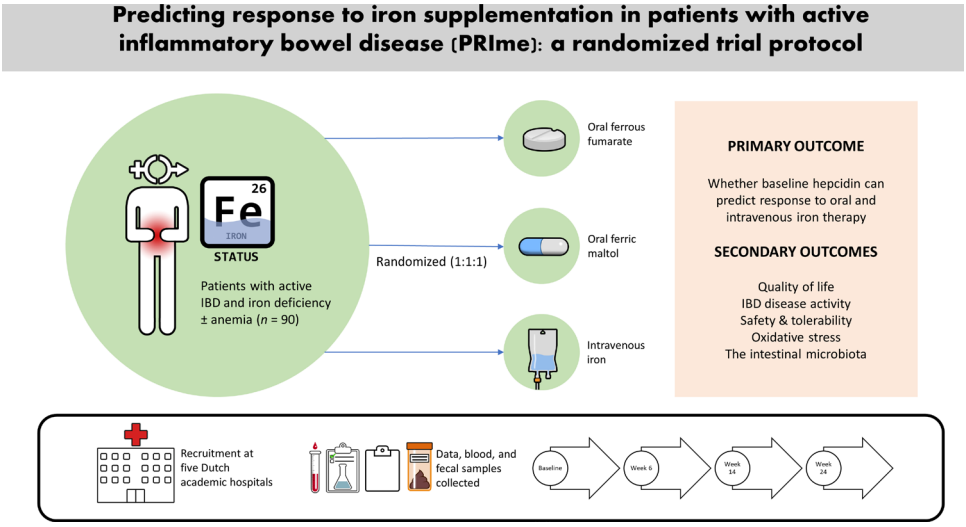

Figure 1 Graphical abstract.

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.

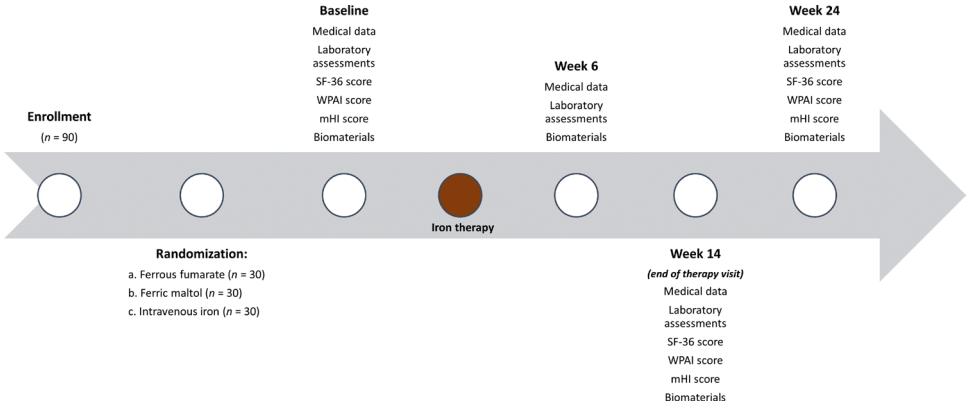

Figure 2 The PRIme trial. mHI, mobile Health Index questionnaire for assessing clinical inflammatory bowel disease activity and burden; SF-36, Short Form 36 questionnaire for evaluating quality of life; WPAI, Work Productivity and Activity Impairment questionnaire. Biomaterials such as blood and faecal 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.

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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.

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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.

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