Feraccru® Real World Effectiveness Study in Hospital Practice (FRESH): A real world study to describe the outcomes associated with the use of ferric maltol (Feraccru®) for the management of iron deficiency anaemia in patients with inflammatory bowel disease in the UK

STUDY PROTOCOL

Sponsor Study Number ST10-01-401

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Date: 3 March 2017

Version: FINAL 2.0

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
CD	Crohn's disease
CRP	C-reactive protein
eDCF	Electronic data collection form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FRESH	Feraccru® Real World Effectiveness Study in Hospital Practice
GafRECGI	Governance Arrangements for Research Ethics Committees Gastrointestinal
Hb	Haemoglobin
HBI	Harvey-Bradshaw Index
HRA	Health Research Authority
IBD	Inflammatory bowel disease
IDA	Iron deficiency anaemia
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
MAH	Marketing Authorisation Holder
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
OFPs	Oral ferrous products
QoL	Quality of life
R&D	Research and Development
REC	Research Ethics Committee
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SCCI	Simple Clinical Colitis Index
SDV	Source data verification
UC	Ulcerative colitis
WHO	World Health Organization

List of definitions

Baseline is defined as the date of initiation of Feraccru®.

Iron deficiency anaemia is defined by the World Health Organization (WHO) as <12.0 g/dL in women and <13.0 g/dL in men[1].

Mild to moderate iron deficiency anaemia (secondary to either CD or UC) is also defined in this study as serum ferritin concentration <30 microgram/L or transferrin saturation of <20%.

Normalised hameoglobin (Hb) is defined in this study as Hb ≥12.0 g/dL for females and ≥13.0 g/dL for males.

Normalised serum ferritin is defined in this study as serum ferritin concentration ≥30 microgram/L and ≤300 microgram/L.

Normalised transferrin saturation is defined in this study as transferrin saturation between 20% and 50%.

Observation period is defined as 12 weeks after initiation of Feraccru® (permitting a window from 10 to 16 weeks).

1. Study synopsis

Title	Feraccru® Real World Effectiveness Study in Hospital Practice (FRESH): A real world study to describe the outcomes associated with the use of ferric maltol (Feraccru®) for the management of iron deficiency anaemia in patients with inflammatory bowel disease in the UK.
Background and rationale for study	Approximately 20–75% of patients with inflammatory bowel disease (IBD) experience iron deficiency anaemia (IDA), which impacts on patients' quality of life (QoL) through a range of symptoms. Oral ferric maltol (Feraccru®) is a novel iron complex licensed in the UK for the treatment of IDA in patients with IBD. Since its launch in 2016, Feraccru® has been used in some secondary care gastroenterology centres. Due to its high bioavailability and better tolerability compared with ferrous iron salt complexes, Feraccru® is likely to be used in patients after failure of oral ferrous products (OFPs), with the aim of preventing the need for IV iron infusions. In the phase III clinical trial, approximately 70% of patients had normalised haemoglobin (Hb) levels after 12 weeks of treatment with Feraccru®. The aim of the study is to understand the early experiences of Feraccru® in patients with IBD and IDA in the UK, including treatment effectiveness, patterns of use and tolerability. By describing the characteristics of patients treated with Feraccru® and their outcomes, this study will provide the medical community with important information to support treatment decisions for their patients. This will ultimately support improvements to patient care, including the long-term outcomes of patients with IBD and IDA.

Objectives	**Primary objective:**
	• To describe the percentage of patients with normalised Hb levels at 12 weeks after initiation of Feraccru®.
	
	Secondary objectives:
	• To describe the clinical outcomes associated with the use of Feraccru® in the real world, including:
	  ○ Change in Hb levels at 4 and 12 weeks after initiation of Feraccru®
	  ○ Time to normalisation of Hb levels after initiation of Feraccru®
	  ○ Change in serum ferritin levels at 4 and 12 weeks

	after initiation of Feraccru® ○ Percentage of patients with normalised ferritin levels at 12 weeks after initiation of Feraccru® ○ Time to correction of serum ferritin levels after initiation of Feraccru® ○ Change in transferrin saturation at 4 and 12 weeks after initiation of Feraccru® ○ Percentage of patients with normalised transferrin saturation at 12 weeks after initiation of Feraccru® ○ Time to correction of transferrin saturation after initiation of Feraccru® • To describe the characteristics of patients receiving Feraccru® in the real world, including: ○ Age and sex ○ Type of IBD ○ Haematology and biochemistry parameters at baseline ○ Time from diagnosis of IBD to initiation of Feraccru® ○ Time from diagnosis of IDA to initiation of Feraccru® ○ Iron treatment history ○ Reason(s) for discontinuing each prior oral ferrous product ○ Reason(s) for initiating Feraccru® ○ Percentage of patients who discontinue Feraccru® ○ Reason(s) for discontinuing Feraccru® ○ Type, severity and time of adverse events that are related to and caused by (in the clinician's opinion) Feraccru®, from initiation of Feraccru®
Hypothesis statement	As the study is descriptive in nature there is no *a priori* hypothesis to be tested.
Study design	An observational, multi-centre cohort study will be conducted in five secondary care gastroenterology centres in the UK. Patients who are prescribed Feraccru® in routine practice will be identified by their care team and approached and asked to provide consent to allow their medical records to be used in the study. There will be no change to the management of patients as a result of taking part in the study. No additional patient investigations or tests will be required. In order to maximise the number of eligible patients, there will be two methods of patient identification and consent: • Retrospective recruitment - Patients initiated on Feraccru® since June 2016 will be approached and asked to provide consent either by post, or when they return

	to clinic for routine follow-up visits. • Prospective recruitment - Patients initiated on Feraccru® during the study period will be identified and asked to provide consent at the time of Feraccru® initiation.
Data source(s)	Data will be collected from hospital medical records, by a member of the care team or a researcher in the study centre.
Number of centres	Five secondary care centres in the UK.
Number of subjects	Approximately 100 patients with IBD (Crohn's disease [CD] or ulcerative colitis [UC]) who are also diagnosed with IDA.
Study time period	12 weeks (permitting a window from 10 to 16 weeks to allow for routine follow up clinic visits to occur).
Patient selection	**Inclusion criteria** • Male and female patients aged ≥ 18 years at the time of initiation • Patient presenting with mild to moderate IDA that is secondary to either CD or UC defined as: o Hb <12.0 g/dL in females o Hb <13.0 g/dL in males o Serum ferritin concentration <30 microgram/L or transferrin saturation of <20% • Patient receiving Feraccru® since the time of UK launch in June 2016 **Exclusion criteria** • Patient receiving Feraccru® as part of an interventional clinical trial • Patients with severely active IBD or requiring corticosteroids at the time of initiation on Feraccru® • Patient with an IBD flare, as determined by the clinician • Patient with medical records that are not available for review • Patient not willing or unable to consent to study participation, or patient is deceased at the start of data collection period
Study endpoints	**Primary endpoint:** • Percentage of patients with normalised Hb levels at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® **Secondary endpoints:** • Descriptive analyses summarising change from baseline

	(permitting a window from -2 to 2 weeks) in Hb levels at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® • Time to normalisation of Hb levels after initiation of Feraccru® • Descriptive analyses summarising change from baseline (permitting a window from -2 to 2 weeks) in ferritin levels at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® • Percentage patients with normalised ferritin levels at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® • Time to correction of serum ferritin levels after initiation of Feraccru® • Descriptive analyses summarising change from baseline (permitting a window from -2 to 2 weeks) in transferrin saturation at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® • Percentage of patients with normalised transferrin saturation at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®. Normalised transferrin saturation is defined as transferrin saturation between 20% and 50% • Time to correction of transferrin saturation after initiation of Feraccru® • Patient characteristics: age, sex and type of IBD • Descriptive analyses of haematology and biochemistry parameters at baseline • Time from diagnosis of IBD to initiation of Feraccru® • Time from diagnosis of IDA to initiation of Feraccru® • Descriptive analyses of prior IV iron treatment, to include at least the percentage of patients with one or more prior infusions • Reason(s) for discontinuing each prior oral ferrous product • Reason(s) for initiating Feraccru® • Percentage of patients who discontinue Feraccru® • Reason(s) for discontinuing Feraccru® • Type, severity and time of adverse events that are related to and caused by (in the clinician's opinion) Feraccru®, from initiation of Feraccru®

Statistical considerations	Given the descriptive nature of the study, a preliminary estimation of the required sample size is expressed in terms of precision and not statistical power. The estimated percentage of patients treated with Feraccru® and a reported normalised Hb at 12 weeks is approximately 66%. The accuracy of this point estimate will vary according to the number of participants in the study. Based on this estimate, precision can be calculated using a Binomial confidence interval. With a sample size of 100 patients, the precision of the estimates is between 9–10%. This means that the percentage of patients treated with Feraccru® with a reported normalised Hb at 12 weeks will be within 9–10% of the true population percentage. Data from all centres will be pooled for analysis. The planned analysis will be descriptive in nature.
Regulatory, ethical and administrative obligations	In line with the harmonised edition of the Governance Arrangements for Research Ethics Committees (GAfREC) (effective from 1st September 2011), this study is required to be submitted for NHS REC review, as it is an observational research study involving collection of non-identifiable information by an external data collector. Consent will be sought from patients and only those who consent will be included in the study.

2. Study amendments and protocol deviations

All amendments to the protocol will be documented in Table 1. Protocol deviations will be documented in a Protocol Deviation Log.

Table 1 Study amendments

Amendment number	Date of amendment	Amendment description	Reason for amendment

3. Background and rationale

Ulcerative colitis (UC) and Crohn's disease (CD) are both types of inflammatory bowel disease (IBD) that are characterised by symptoms of bloody diarrhoea, abdominal pain and cramps[2]. Anaemia is a complication that occurs in up to 70% of patients with CD or UC[3–6]. Iron deficiency anaemia (IDA) is the most common cause of anaemia in these patients.

Iron deficiency can result from insufficient dietary intake, chronic inflammation reducing absorption, malabsorption and/or intestinal bleeding[3,7–9]. In IBD, iron deficiency results from a combination of functional iron deficiency due to inflammation and chronic blood loss[10]. Approximately 20–75% of patients with IBD experience IDA[3,5,11], which can impair patients' quality of life (QoL) through symptoms such as fatigue, dizziness, headache, tachycardia, shortness of breath, depression, and reduced cognitive functioning[5,12]. Not only does IDA in IBD have a considerable impact on activities of daily living, but severe symptoms can lead to hospitalisation. Iron deficiency anaemia is defined by the World Health Organization (WHO) as haemoglobin (Hb) <12.0 g/dL in women and Hb <13.0 g/dL in men[1]. Laboratory investigations using modern automated cell counters are able to detect changes in red cell indices, including reduced mean corpuscular volume (MCV) and reduced mean corpuscular haemoglobin (Hb) (MCH), necessary for a diagnosis of IDA[13].

Treatment goals in the clinical management of IDA are to normalise Hb concentrations and red cell indices, as well as replenishing iron stores. Clinical guidelines recommend the inclusion of oral iron supplementation to correct anaemia, with oral iron continued for 3 months after the IDA has been corrected[14,15]. Guidance also suggests regular patient monitoring; every 3 months up to a year after IDA correction then 12 months thereafter, and again if symptoms of anaemia develop[14]. For patients who are intolerant, or have an insufficient response to oral iron, intravenous (IV) iron is recommended which is often administered in a hospital setting as a day case. This results in an increased burden on patients and increased costs associated with both the drug and use of hospital services[14].

Oral ferric maltol (Feraccru®) is a novel iron complex consisting of a single ferric iron ion (Fe3+), chelated with high affinity to three maltol molecules. Maltol is a natural sugar derivative that binds with high affinity to ferric iron until it is released directly into the area of the gastrointestinal (GI) tract where it is best absorbed. This is suggested to confer high

bioavailability and better tolerability compared with ferrous iron salt complexes, due to the reduced exposure of free iron throughout the GI tract. Feraccru® is licensed in the UK for the treatment of IDA in patients with IBD and has been used in a number of secondary care gastroenterology centres since its launch in 2016. Feraccru® is likely to be used in patients after failure of oral ferrous products (OFPs), with the aim of preventing the need for intravenous (IV) iron infusions. In the phase III clinical trial, approximately 70% of patients had normalised haemoglobin after 12 weeks of treatment with Feraccru®[3].

3.1 Rationale for study

As Feraccru® has only been on the UK market for a relatively short period of time, real world evidence is required to understand early experiences of Feraccru® in IBD patients with IDA in UK routine practice. For example, data are needed to determine whether biochemical outcomes seen in clinical trials can be replicated in a more diverse and representative population in the real world. Information is also needed about the characteristics and treatment history of patients who receive Feraccru®, and the tolerability that is achieved. By describing the characteristics of patients treated with Feraccru® and their associated outcomes, this study will provide the medical community with important information to support their treatment decisions for their patients. The findings from this study will ultimately support improvements to patient care, including the long-term outcomes of patients with IBD and IDA.

4. Aim and objectives

4.1 Aim

To describe the real-world use of Feraccru®, and the characteristics and the clinical outcomes of patients with IBD and IDA who receive Feraccru®.

4.2 Primary objective

To describe the percentage of patients with normalised Hb levels at 12 weeks after initiation of Feraccru®.

4.3 Secondary objectives

- To describe the clinical outcomes associated with the use of Feraccru® in the real world, including:
    - Change in Hb levels at 4 and 12 weeks after initiation of Feraccru®
    - Time to normalisation of Hb levels after initiation of Feraccru®
    - Change in serum ferritin levels at 4 and 12 weeks after initiation of Feraccru®
    - Percentage of patients with normalised ferritin levels at 12 weeks after initiation of Feraccru®
    - Time to correction of serum ferritin levels after initiation of Feraccru®
    - Change in transferrin saturation at 4 and 12 weeks after initiation of Feraccru®
    - Percentage of patients with normalised transferrin saturation at 12 weeks after initiation of Feraccru®
    - Time to correction of transferrin saturation after initiation of Feraccru®
- To describe the characteristics of patients receiving Feraccru® in the real world, including:
    - Age and sex
    - Type of IBD
    - Haematology and biochemistry parameters at baseline
    - Time from diagnosis of IBD to initiation of Feraccru®
    - Time from diagnosis of IDA to initiation of Feraccru®
    - Iron treatment history
    - Reason(s) for discontinuing each prior oral ferrous product
    - Reason(s) for initiating Feraccru®
    - Percentage of patients who discontinue Feraccru®
    - Reason(s) for discontinuing Feraccru®

- Type, severity and time of adverse events that are related to and caused by (in the clinician's opinion) Feraccru®, from initiation of Feraccru®

5. Hypothesis

As the study is descriptive in nature, there is no *a priori* hypothesis to be tested.

6. Study design and methodology

The study has been designed and will be conducted according to the requirements of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/index.shtml) and International Society for Pharmacoepidemiology (ISPE; https://www.pharmacoepi.org/resources/guidelines_08027.cfm) guidance, as appropriate.

This study will be an observational, multi-centre cohort study conducted in five secondary care NHS centres across the UK. Patients will be recruited using both retrospective and prospective approaches.

6.1 Study time periods

Eligible patients will be followed from the time of initiation on Feraccru® for 12 weeks, with a permitted window from 10 to 16 weeks.

6.2 Study population

The study population will be patients under the management of secondary care gastroenterology centres in the UK that are using Feraccru®. Study participants will be required to consent to study participation by the signing of a consent form before any data are collected.

The study sample will be derived from the population of patients with IBD (either CD or UC) who also have a clinically confirmed diagnosis of IDA and were either:

- Initiated on Feraccru® since June 2016 (retrospectively recruited patients), or
- Initiated on Feraccru® during the study period (prospectively recruited patients).

6.2.1 Inclusion criteria

- Male and female patients aged ≥ 18 years at the time of initiation
- Patients presenting with mild to moderate IDA that is secondary to either CD or UC, defined as;
    - Hb <12.0 g/dL in females
    - Hb <13.0 g/dL in males
    - Serum ferritin concentration <30 microgram/L or transferrin saturation of <20%
- Patients receiving Feraccru® since the time of UK launch in June 2016

6.2.2 Exclusion (ineligibility) criteria

- Patient receiving Feraccru® as part of an interventional clinical trial
- Patients with severely active IBD or requiring corticosteroids at the time of initiation on Feraccru®
- Patient with an IBD flare, as determined by the clinician
- Patient with medical records that are not available for review
- Patient not willing or unable to consent to study participation, or patient is deceased at the start of data collection period.

6.2.3 Participant recruitment

Patients who are prescribed Feraccru® and eligible for inclusion in the study will be identified by their care team and approached and asked to provide consent to allow their

medical records to be used in the study. There will be no change to the management of patients as a result of taking part in the study. No additional patient investigations or tests will be required. In order to maximise the number of eligible patients, there will be two methods of patient identification and consent;

1. Retrospective recruitment - Patients who were initiated on Feraccru® since its launch in June 2016 will be approached and asked to complete a consent form either by post or when they return to the gastroenterology clinic for routine follow-up visits.
2. Prospective recruitment - Patients initiated on Feraccru® during the study period will be identified and asked to provide consent (and complete a consent form) at the time of Feraccru® initiation.

The study will recruit approximately 100 patients across 5 centres.

6.3 Data collection

Patients will be identified in all study records using a unique study code, which will allow individual patients to be identified for each of their clinic visits and allow data queries to be raised with centres by the data management team at pH Associates while preserving patient confidentiality. Further information on data collection can be found in section 7.

Data relating to the patient's demographics, IDA treatment history, outcomes, and tolerability of Feraccru®, will be collected by a member of the care team, or a researcher in the study centre. Data will be entered onto electronic (MACRO) data collection forms (eDCF) designed specifically for the study.

6.4 Data source

The study data will be derived from hospital medical records. This will include, but not be limited to case notes, prescribing records, laboratory reports and investigation reports.

6.5 Study endpoints and variables

6.5.1 Primary endpoint

- Percentage of patients with normalised Hb levels at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru® (normalisation of Hb defined as Hb ≥12 g/dL for females and ≥13.0 g/dL for males)

6.5.2 Secondary endpoints

- Descriptive analyses summarising change from baseline (permitting a window from -2 to 2 weeks) in Hb levels at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®
- Time to normalisation of Hb levels (normalisation of Hb defined as Hb≥ 12 g/dL for females and ≥13.0 g/dL for males) after initiation of Feraccru®
- Descriptive analyses summarising change from baseline (permitting a window from -2 to 2 weeks) in ferritin levels at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®
- Percentage of patients with normalised ferritin levels at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®. Normalised serum ferritin is defined as serum ferritin concentration ≥30 microgram/L and ≤300 microgram/L
- Time to correction of serum ferritin levels after initiation of Feraccru®
- Descriptive analyses summarising change from baseline (permitting a window from -2 to 2 weeks) in transferrin saturation at 4 weeks (permitting a window from 3 to 5 weeks) where data are available, and 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®
- Percentage of patients with normalised transferrin saturation at 12 weeks (permitting a window from 10 to 16 weeks) after initiation of Feraccru®. Normalised transferrin saturation is defined as transferrin saturation between 20% and 50%

- Time to correction of transferrin saturation after initiation of Feraccru®
- Patient characteristics: age, sex and type of IBD
- Descriptive analyses of haematology and biochemistry parameters at baseline
- Time from diagnosis of IBD to initiation of Feraccru®
- Time from diagnosis of IDA to initiation of Feraccru®
- Descriptive analyses of prior IV iron treatment, to include at least the percentage of patients with one or more prior infusions
- Reason(s) for discontinuing each prior oral ferrous product
- Reason(s) for initiating Feraccru®
- Percentage of patients who discontinue Feraccru®
- Reason(s) for discontinuing Feraccru®
- Type, severity and time of adverse events that are related to and caused by (in the clinician's opinion) Feraccru®, from initiation of Feraccru®

6.5.3 Variables to be collected

The following study variables will be collected during the observation period to measure the study endpoints, in order to describe the use of Feraccru® in the real world.

Patient demographics and other characteristics:

- Age at initiation of treatment with Feraccru®
- Sex (Male/Female)
- Date diagnosed with IBD
- Type of IBD (CD/UC)
- Date diagnosed with IDA
- Description of IV iron treatment history, to include at least the number of prior infusions
- Description of oral iron treatment history, where available in secondary care notes

- Experience of oral ferrous products (OFPs) (Yes/No), if yes:
- Name(s) of OFP(s)
- Reason(s) for discontinuing OFP(s)

Feraccru® treatment:

- Date initiated on Feraccru®
- Reason(s) for initiating Feraccru®
- Date discontinued Feraccru®
- Reason (s) for discontinuation of Feraccru®

Haematology and biochemistry parameters:

The date(s) and result(s) of haemoglobin (Hb), ferritin and transferrin saturation will be collected from baseline (permitting a window from -2 to 2 weeks) to 12 weeks (permitting a window from 10 to 16 weeks). The date(s) and result(s) of the following haematology and biochemistry parameters will be collected at baseline only (permitting a window from -2 to 2 weeks):

- Folate
- B12
- Mean corpuscular volume
- Mean corpuscular Hb
- Platelets
- C-reactive protein (CRP)

Adverse events:

The details of adverse events (AEs) that are considered to be related to Feraccru® treatment, determined by clinical opinion, will be collected:

- Type, severity, start and end dates of AE/serious adverse event (SAE) with a temporal relationship to and caused by Feraccru®, as determined by the clinician

7. Data management and quality control

Data collection will be completed by trained staff employed by the NHS Trust or staff from pH Associates. All data collectors will be provided with Data Collection Guidelines to provide further information regarding the completion of the electronic Data Collection Form (eDCF). The same data collector will be used at each centre, wherever possible, to ensure consistency in data collection, if feasible. All data collected will be submitted regularly in anonymised-coded form to pH Associates for data entry, cleaning and analysis.

7.1 Database management

The eDCF will be developed from a paper draft and then converted to electronic form in MACRO, which is a web-based secure electronic data capture and data management tool. MACRO is compliant with FDA 21 CFR part 11 and Good Clinical Practice (GCP) and has been widely used in the UK NHS for complex interventional clinical trials and used by pH Associates on a range of real world evidence studies. A data analysis tool will be developed using Microsoft capabilities (Access®, Excel®).

7.2 Data quality checks

As this study will use both retrospective and prospective methods of data collection, the quality of the study dataset will depend on the accuracy and completeness of data recorded in patients' medical records. Where data on study variables are not available, fields will be marked as 'not known' rather than left empty. Quantitative data collected for laboratory (haematology and biochemistry) parameters will be standardised per centre using laboratory reference ranges entered on the eDCF. This will allow pooling of these study parameters across centres.

All data submitted will be checked for accuracy and completeness. Queries will be raised by the pH Associates data management team. Study centres will be required to co-operate with the data management team in the resolution of these queries. On completion of the first three eDCFs from at least two centres, a pilot data review will be completed. This pilot will ensure that the study dataset can be captured feasibly and efficiently on the eDCF and the methodology for data collection is suitably robust.

In order to confirm the accuracy and quality of the data, source data verification (SDV) will be completed for a randomly selected 10% of all patients. 100% of the data collected for these patients will be reviewed by pH Associates staff. Where data collection is completed by pH Associates staff, the staff member who carries out the SDV will be different to the person responsible for data collection at that specific centre.

8. Study sample size

Given the descriptive nature of this study, a preliminary estimation of the required sample size is expressed in terms of precision and not statistical power. In the literature, the percentage of patients treated with Feraccru® with reported normalised Hb at 12 weeks is approximately 66%[3]. However, the accuracy of such estimates will vary according to the number of participants in the study. Using 66% as the percentage of patients expected to show a normalised Hb at 12 weeks, the precision of such estimates can be calculated using a Binomial confidence interval (Table 2).

Table 2 Precision calculated using a Binomial confidence interval (Wald interval, normal approximation)

Patients with normalised Hb at 12 weeks (%)	Precision (%)	Study patients (N)
66%	7%	176
66%	8%	135
66%	9%	107
66%	10%	87
66%	11%	72
66%	12%	60

With a sample size of 100 patients, the precision of the estimates is calculated as between 9–10%. This means that the percentage of patients treated with Feraccru® with a reported normalised Hb at 12 weeks in the study will be within 9–10% of the true population percentage.

9. Statistical analysis

Analyses will be performed by pH Associates. The planned analysis will be descriptive in nature. Both distributions and descriptive statistics of central tendency (arithmetic means and medians) and dispersion (standard deviation, interquartile range) will be presented for quantitative variables. Nominal variables will be described with frequencies, percentages and modes, while ordinal variables will also have medians and interquartile ranges described. Confidence intervals will be provided for means of quantitative variables.

9.1 Missing data

Whilst study centres will be selected to include those expected to have the most complete data, this study involves the retrospective collection of data from medical records. As such,

it is possible that some data points will be missing. Where data are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available (complete case analysis) and the number of patients included in each analysis will be stated. The percentage of data missing will be reported for each study variable. Missing data in itself will be of interest and should provide insight into the way patients are being managed in the UK outside the methodological constraints of a clinical trial.

10. Review of study results

No independent review of statistical data/study results is planned prior to completion of the study report. Investigators will be able to review the study results at the investigator meeting.

11. Study limitations

The quality of the dataset may be limited by the accuracy and completeness of patients' medical records. It is believed that this limitation will be minimised by robust feasibility testing of the protocol framework during its development and additional evaluation during site selection. Furthermore, training of all data collectors and source data verification will ensure high quality data and will minimize potential bias.

12. Safety

12.1 Definitions

12.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

Adverse drug reactions (ADRs) are a subset of AEs where there is a clear causal relationship between the treatment and the event. This study requires the collation of all AEs, including ADRs.

12.1.2 Serious adverse events

An adverse event is considered serious (SAE) if it:

- Is fatal
- Is life threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other significant medical hazard

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

A serious adverse drug reaction (SADR) is a serious adverse event that is considered related to the medicinal product. A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

12.2 Reporting procedures for adverse events

All SAEs/Special Reporting Situations related to any Shield Therapeutics PLC product(s) at each centre shall be reported to PrimeVigilance Limited by the Principal Investigator /pH Associates within 24 hours of discovery or notification. Initial SAE information and all follow-up information must be recorded on the SAE form and emailed to PrimeVigilance Limited. Investigators may be requested to provide follow-up information concerning serious adverse events, including an evaluation of causality and seriousness. Relatedness of the SAE to Shield Therapeutics PLC product(s) will be assessed by the investigator if there is doubt.

All non-serious AEs will be captured as part of the study dataset and will be tabulated in the study report but will not be subject to expedited reporting. Only SAE and AEs judged to be related to Feraccru® will be included as a study endpoint. As all adverse events will be documented (and ultimately made available to the Medicines and Healthcare products Regulatory Agency, MHRA) by Shield Therapeutics PLC as study sponsor, there is no need for investigator sites to duplicate adverse event reporting through the Yellow Card Scheme.

12.3 Special Reporting Situations

Any AEs in the following patient groups should be reported as if it was an SAE to PrimeVigilance Limited.

- Pregnancy: Any case in which a patient is found to be pregnant or to have become pregnant following treatment with the Product(s). Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: infant exposure from breastfeeding.

- Overdose: All information of any accidental or intentional overdose.
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual).
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of effect report for the product(s).
- Any use of the product in children.
- Occupational exposure.
- Use outside the terms of the marketing authorization, also known as "off-label".
- Use of falsified medicinal product.
- Use of counterfeit medicinal product.

SAFETY CONTACT DETAILS

PrimeVigilance Limited has been contracted by the Sponsor for safety reporting

Email SAE reports to shieldpv@primevigilance.com or fax to +44 (0)1483 431831

and copy to data@phassociates.com

13. Ethical and regulatory obligations

13.1 Protection of human subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

As this is an observational study, there is no additional risk to participants as all data are collected from medical records and patients will have no direct involvement in the study with the exception of providing their informed consent for data to be collected from their medical records. There will be no change to the management of patients as a result of taking part in the study.

In accordance with the UK Department of Health Research Governance Framework for Health and Social Care this type of study, except in specific cases, must be submitted for review by an independent committee. This study will therefore be submitted for review by

an NHS Research Ethics Committee (REC), via the Health Research Authority (HRA). The study will also be submitted for inclusion in the NIHR portfolio of research studies. NHS management approval for local conduct of the study and the sharing of anonymised- coded patient data will be sought via the Research and Development (R&D) department in each participating Trust.

14. Study timelines

Table 3 Study timelines

Study milestone	**Expected date(s)/frequency**
Start of data collection	May 2017
End of data collection	August 2017
Data analysis	August to September 2017
Final report of study results	October to November 2017

15. Administrative and legal obligations

15.1 Study amendments and study termination

Amendments must be made only by prior agreement between Shield Therapeutics PLC, pH Associates and Dr Fraser Cummings. The REC must be informed of all amendments and give approval for substantial amendments. The Chief Investigator must send a copy of the approval letter from the REC to Shield Therapeutics PLC. pH Associates, Shield Therapeutics PLC, and the investigator reserve the right to terminate participation in the study according to the study contract. pH Associates will notify the REC in writing of the study's completion or early termination and send a copy of the notification to Shield Therapeutics PLC and the Chief Investigator.

15.2 Study documentation and archive

Completed eDCFs are transmitted over a secure connection to pH associates in real time. The principal investigator (PI) at each site must ensure that information entered in the eDCF is traceable to the source documents in the patient's medical record (paper or electronic). Changes to the eDCF are recorded in the MACRO audit trail, these include changes in response to queries, SDV and data entry errors.

The study documentation and electronic data will be kept after the study for 5 years and will then be securely destroyed according to the policy of the sponsor.

15.3 Ethical and regulatory approvals

In line with the harmonised edition of the Governance Arrangements for Research Ethics Committees (GAfREC) (effective from 1st September 2011), this study is required to be submitted for NHS REC review, as it is an observational research study involving collection of non-identifiable information collected by an external data collector. Consent will be sought from patients and only those who consent will be included in the study.

Clinical trials in the UK are regulated and require authorisation by the UK competent authority, Medicines and Healthcare Products Regulatory Agency (MHRA). This non-interventional study does not require authorisation, as The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031) do not apply.

15.4 Ethical issues

Patients with IBD and IDA who have been identified as being eligible for study participation will be provided with a patient information sheet and consent form by a member of their care team. This will provide written information for their consideration and discussion with their family and friends and as well as care team members. The patient will be allowed adequate time to consider whether they wish to consent for their participation in the study and have any questions answered by their care team.

No patient identifiable information will be collected or removed from the NHS Trusts participating in the study in order to preserve patient confidentiality. Patients will be assigned a study-specific patient number which will be referenced in a study log. This patient log will not leave the participating NHS Trust and will be the responsibility of the principal investigator at that study centre.

16. Communication of study results

The study will be reported according to the requirements of STROBE (Strengthening the reporting of observational studies in epidemiology) as specified in the appropriate checklist for the study design (http://www.strobe-statement.org/index.php?id=available-checklists).

Authorship of publications arising from the study will follow the guidelines proposed by the International Committee of Medical Journal Editors (2015) (http://www.icmje.org/icmje-recommendations.pdf). All authors will meet the criteria for authorship, and all people who meet the criteria will be authors. Potential conflicts of interest will be disclosed. All authors will have:

(1) made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND

(2) participated in drafting the article or revising it critically for important intellectual content; AND

(3) approved the final version to be published.

Each author will meet all of these conditions and all individuals meeting these criteria will be authors. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

17. Study support

The study is sponsored by Shield Therapeutics PLC, the manufacturer of Feraccru®. Shield Therapeutics PLC have commissioned pH Associates Ltd to develop materials for and co-ordinate the conduct of the study, including protocol development, ethical and local approval, retrospective data collection, analysis and presentation of the results. pH Associates is an independent consultancy specialising in the evaluation of healthcare services and interventions in the NHS through observational research, with a focus on the design and implementation of 'Real World Data' projects in order to understand current NHS practices.

18. References

1. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr. 2009 Apr;12(4):444–54.

2. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009 Nov 19;361(21):2066–78.

3. Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Buning C, et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. Inflamm Bowel Dis. 2015 Mar;21(3):579–88.

4. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol. 2010 Nov;7(11):599–610.

5. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. Aliment Pharmacol Ther. 2006 Dec;24(11–12):1507–23.

6. Gasche C, Beguin Y, de Silva A. IBD and anemia. In: Anemia in Inflammatory Bowel Diseases. Bremen: UNI-MED Verlag AG; 2008.

7. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005 Mar 10;352(10):1011–23.

8. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007 Aug 11;370(9586):511–20.

9. Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis. 2007 Dec;13(12):1545–53.

10. Weiss G, Gasche C. Pathogenesis and treatment of anemia in inflammatory bowel disease. Haematologica. 2010 Feb;95(2):175–8.

11. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004 Oct 15;104(8):2263–8.

12. Gasche C, Lomer MCE, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004 Aug;53(8):1190–7.

13. Lewis S, Bain B, Bates I. Dacie and Lewis Practical Haematology. 9th ed. London: Churchill Livingstone; 2001.

14. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut. 2011 Oct;60(10):1309–16.

15. Smith A. Prescribing iron. Prescribers' J. 1997;37:82–7.