Research Protocol

RAndomised IroN Deficiency anaemia management Pilot

Study Acronym	RAINDroP
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RAINDroP: RAndomised IroN Deficiency anaemia management Pilot

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

Professor Phyo K Myint

Chief Investigator _____ Signature _____ Date

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S.1 LAY SUMMARY

Anaemia due to low iron levels is common in older people and can cause tiredness and breathlessness. It is commonly treated with oral iron supplementation. However, oral iron supplementation does not improve anaemia in many people and they may have side effects. We do not know what strategy of care is best for patients who do not respond to oral iron supplementation: should we stop treatment, continue with supplementation (which is current practice) or switch to iron given by a drip (intravenous iron)?

We will conduct a pilot randomised controlled trial to identify what is the best way of finding and recruiting people who do not respond to oral iron supplementation, and to compare the three current strategies of care. We will recruit 84 older people with iron deficiency anaemia who are not improving on oral iron supplementation, and randomise them to receive one of the above three strategies of care for three months.

Key outcomes will include: how long it takes to recruit enough people to the study, which method(s) of recruitment (clinic, adverts or GP letters) is/are most efficient, and the improvement in haemoglobin level (a measure of anaemia) in each treatment arm.

The results will allow us to plan a large, multicentre trial to find out which of the three options should become routine clinical care in this situation.

S.2 SCIENTIFIC SUMMARY

Anaemia is a common problem, and is particularly common in older people. It is associated with fatigue, impaired functional capacity, increased hospitalization and mortality. In the USA, the prevalence of anaemia as defined by the World Health Organisation (Hb <130g/L in men and <120g/L in women) among community-dwelling adults age 65 years and older was 11.0% and 10.2% in men and women, respectively, rising to more than 20% in those >85 years.

In this pilot study we will recruit older people, aged 65 years or over, with mild-moderate iron deficiency anaemia (anaemia defined as haemoglobin (Hb) between 85 and 110 g/L and iron deficiency defined as ferritin <100µg/L prior to commencing oral iron) and who show insufficient response to oral iron therapy (sufficient response defined as improvement in Hb by 20g/L within 3 months of commencement of oral iron therapy) into a three-arm study. The study arms are:

- Treatment as usual
- Stop oral iron treatment
- Stop oral iron and give IV iron (as per local formulary).

The co-primary outcomes are:

1) the rate of randomisation per month across the pilot sites
2) the proportion recruited from each route of recruitment

Secondary outcomes are:

1) change in haemoglobin and ferritin levels at 3 months
2) number of eligible patients per site
3) proportion of eligible patients agreeing to take part and passing screening
4) feasibility of collecting primary (physical functioning and health-related and general quality of life) and secondary outcomes for main trial:
    - Short physical performance battery
    - Six-minute walk distance
    - Anaemia-related symptoms (e.g. breathlessness, tiredness, fatigue)
    - Health-related quality of life (EQ-5D-5L™, 15D©)
    - Activities of daily living (NEADL©)
    - Health care use including use of blood transfusions and hospitalisation
    - All-cause mortality
5) dropout rate at 3 months; crossover rate at 3 months

6) reported side effects and adverse events (GI symptoms, headache, dizziness, rash)
7) functional limitation (six-minute walk <400m or short physical performance battery ≤10)
8) level of fatigue assessed using validated Fatigue Severity Scale
9) Patient experience.
10) Oral Iron Use Likert Scale (in those taking oral iron only)
11) Participant experience using semi-qualitative questionnaire.

Table 1: List of abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
CI	Chief Investigator
Co-CI	Co-Chief Investigator
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GP	General Practitioner
HERA	Health Economics Research Unit (Aberdeen)
HIC	Health Informatics Centre (Dundee)
HRA	Health Research Authority
ICF	Informed Consent Form
IDA	Iron Deficiency Anaemia
IMP	Investigational Medicinal Products
ISF	Investigator Site File
ITT	Intention To Treat
IV	Intravenous
NHS	National Health Service
NIHR	National Institute for Health Research
NRS	NHS Research Scotland
PI	Principal Investigator
PID	Personal Identifiable Data
PIS	Participant/Patient Information Sheet
RCT	Randomised Clinical Trial
R&D	NHS Board/Trust R&D Department
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
PCN	Primary Care Network
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
TASC	TAyside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group

1 INTRODUCTION

1.1 BACKGROUND

Anaemia is a common problem and is particularly common in older people. It is associated with fatigue, impaired functional capacity, increased hospitalisation and mortality (1) In the USA the prevalence of anaemia as defined by the World Health Organisation (Hb <130g/L in men and <120g/L in women) (2) among community-dwelling adults age 65 years and older was 11.0% and 10.2% in men and women, respectively (3), rising to more than 20% in those >85 years (4).

Iron deficiency is one of the commonest causes of anaemia. It can be diagnosed by the presence of low ferritin levels or low serum iron and transferrin saturation levels (5). The estimated prevalence of iron deficiency anaemia (IDA) in adult men and post-menopausal women in western countries is 2-5% (5). IDA is especially common in older people (6); it accounts for up to 30% of all cases of anaemia in older adults (7). In Tayside, Scotland, alone approximately 5,000 people over the age of 65 (i.e. ~5% of the population in this age group) received at least one prescription for oral iron in the year 2015-2016. Large numbers of people in Scotland are therefore treated for iron deficiency, many of whom are on long term treatment, making the question of how to treat this condition most effectively an important one for patients, clinicians and healthcare funders.

Despite the widespread use of oral iron to treat even mild IDA in older people, evidence is lacking on the best way to treat this condition, or indeed whether treatment is required at all in mild cases. Our recent systematic review found only three RCTs testing the efficacy of oral iron compared to placebo or no iron. The treatment effect was trivial: haemoglobin levels increased by a mean of only 3.5g/L (95%CI:1.2-5.9g/L) (8). Routinely collected data from older people in Tayside support these findings with most recipients of oral iron showing little or no improvement in haemoglobin levels; many older patients are exposed to oral iron without good evidence of a significant response to therapy (9).

A further problem with the existing evidence is that the available trials did not aim to measure outcomes relevant to older patients – such as symptom improvement or improvement in physical performance, activities of daily living or quality of life (7). Furthermore, a review of the evidence for intravenous iron found no precise comparison of the clinical benefit of different iron preparations (10).

Current practice is to treat older people with iron-deficiency anaemia with oral iron after relevant investigations and management of any treatable causes. Oral iron therapy is aimed at correcting the

deficiency and also to replenish iron storage (11). One reason why oral iron may be ineffective at improving anaemia in many older people is due to the coexistence of other diseases, particularly chronic inflammation and chronic kidney disease. Hepcidin regulates entry of iron into circulation and high hepcidin levels are seen in chronic inflammation. These in combination affect hepcidin pathways with resultant reduction in iron absorption from gut mucosa (6). A second important reason why oral iron may be ineffective relates to the fact that it causes side effects in up to 40% of people - particularly gastrointestinal symptoms (12) with subsequent impact on diet, nutrition and health related quality of life (13, 14). Oral iron is consequently poorly adhered to and thus compliance is an issue with long term therapy. Intravenous iron can overcome both of these problems, but it is more expensive than oral iron and carries a small, but non-trivial risk of anaphylactoid reactions.

Despite this, analysis of routinely collected data from older patients who had undergone inpatient rehabilitation between 1999 and 2011 showed oral iron treatment non-systematic, and lack clear clinical pathways in real world setting (9). In this study (Thomson, Hands and Witham) we found that a total of 490 patients were prescribed oral iron within 90 days of rehabilitation discharge. Of these, 413 (84%) had iron indices performed; 94 (23%) were possibly deficient (transferrin 2.0-2.5g/L, ferritin 50-100µg/L), 224 (54%) were probably deficient (>2.5g/L and <50µg/L), and 95 (23%) were not deficient (>2.0g/L and >100µg/L). Of the 490 patients, 360 had both pre- and post-treatment haemoglobin data and iron indices; neither probably deficient nor possibly deficient patients showed a large improvement in haemoglobin levels, although probably deficient patients mounted a slightly greater response to oral iron (17 vs. 12 g/L for not deficient; $p < 0.05$). This finding of only a weak rise in Hb in this cohort further strengthened the evidence that many older patients are exposed to oral iron without good evidence of a significant response to therapy.

1.2 RATIONALE FOR THE STUDY

A satisfactory response (rise in Hb of 20g/L) to oral iron is usually expected within 6-8 weeks of commencing treatment. The current standard of care is to continue oral iron even if a suboptimal (or no) response is seen. It is unclear if the current standard of care is of value to patients and healthcare providers. The balance of benefit and harm for oral iron in older people is unclear, and the best strategy for those not responding to oral iron is also unclear. Should oral iron be continued for longer, switched to intravenous iron, or simply stopped if it is not working? It is also uncertain whether further oral or IV iron therapy improves physical function and quality of life compared to no therapy in older patients with iron-deficiency anaemia.

We conducted an online survey of geriatricians and GPs in November 2016 through the British Geriatrics Society. Our survey confirmed the uncertainties in managing IDA, evident by inconsistent approaches and lack of clinicians' knowledge on whether the choice of management actually improved patient outcome. Over 85% of respondents stated that they regularly prescribe oral iron in at least 50% of their patients with IDA. 30% of respondents regularly prescribe oral iron in almost all of their patients with IDA. Although >85% who responded were willing to facilitate recruitment of eligible patients into a trial, they indicated some reluctance to discontinue oral iron therapy. Therefore, the proposed trial design needs a pilot study to demonstrate if recruitment is feasible.

We have run focus groups with older people who have IDA and received either oral or IV iron. They identified being symptom-free with improved quality of life and the ability to carry out daily tasks as the most desirable outcomes for therapy. They suggested that potential participants would be willing to receive an invitation letter to participate in the proposed study either from their own GP or their hospital consultant. They were uncertain about the idea of continuing oral iron if it had been ineffective, despite this being current standard practice. No ethical issues or concerns have been raised by clinicians or patients. However, we are aware of potential side effects of IV iron administration and therefore safety outcomes have been included as one of the secondary outcomes in this pilot.

This pilot study is a critical step towards a definitive multicentre trial, which we would plan to submit to the NIHR HTA programme for funding. The definitive multicentre trial would provide the evidence of clinical effectiveness using outcomes most relevant to older people (physical function and quality of life, rather than just relying on haemoglobin measurements) and importantly, of cost-effectiveness – a particular issue with the increasing use of IV iron, which is relatively expensive compared to oral iron.

2 STUDY OBJECTIVES & OUTCOMES

A summary of study objectives and outcomes is provided in Table 2 and Table 3

Table 2: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured:**
To estimate the recruitment rates and examine recruitment strategies at pilot sites across different settings and different NHS providers.	The rate of randomisation per month across all pilot sites.	End of recruitment / End of study.
	The proportion recruited from each route of recruitment which include (i) primary care and secondary care prescription; (ii) blood test results; (iii) through individual clinicians; (iv) from public advertisement; and (v) SHARE database.	End of recruitment / End of study.

Table 3: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured:**
To examine the change in a key surrogate outcome (haemoglobin levels).	Change in haemoglobin levels between baseline and 3 months.	0 & 3 months.
To examine the change in secondary surrogate outcome.	Change in ferritin between baseline and 3 months.	0 & 3 months.
To obtain preliminary data on the proposed patient outcomes (quality of life, symptoms and physical function).	Number of eligible patients per site Proportion of eligible patients agreeing to take part and passing screening. Feasibility of collecting proposed outcomes for a future definitive trial: Short physical performance battery (SPPB) (15) Six-minute walk distance Anaemia-related symptoms Health-related quality of life (EQ-5D-5L™, 15D©) (16) (17) Activities of daily living (NEADL©) (18) Functional limitation (using 6 minute walk & SPPB) Fatigue Severity Scale (19) Oral Iron Use Likert Scale (oral iron only).	0 & 3 months.
	Health care use All-cause mortality Dropout rate at 3 months Crossover rate at 3 months Participant experience semi-qualitative questionnaire.	3 months.

2.1 OBJECTIVES

2.1.1 Primary Objectives

The primary objective of this pilot study is to estimate the recruitment rates and examine recruitment strategies at pilot sites across different settings and different NHS providers.

2.1.2 Secondary Objectives

The secondary objectives are to examine the change in a key surrogate outcome (haemoglobin and ferritin levels) and to obtain preliminary data on the proposed patient outcomes (quality of life, symptoms and physical function) to inform the sample size calculation for a future definitive trial.

2.2 OUTCOMES

2.2.1 Co-Primary Outcomes

1) The rate of randomisation per month across all pilot sites
2) The proportion recruited from each route of recruitment which include:
    - primary care and secondary care oral iron prescriptions
    - NHS electronic blood test results
    - through individual NHS clinicians and GPs
    - from public advertisement and press releases
    - research volunteer databases, including SHARE.

2.2.2 Secondary Outcomes

1) Change in haemoglobin levels between baseline and 3 months
2) Change in ferritin levels between baseline and 3 months
3) Number of eligible patients per site
4) Proportion of eligible patients agreeing to take part and passing screening
5) Feasibility of collecting proposed outcomes at baseline and 3 months for a future definitive trial:
    - Short physical performance battery (15)
    - Six-minute walk distance
    - Anaemia-related symptoms (e.g. breathlessness, tiredness, fatigue)
    - Health-related quality of life (EQ-5D-5L™, 15D©) (16, 17) (20)

- Activities of daily living (NEADL©) (18)
- Health care use including use of blood transfusions and hospitalisation
- All-cause mortality

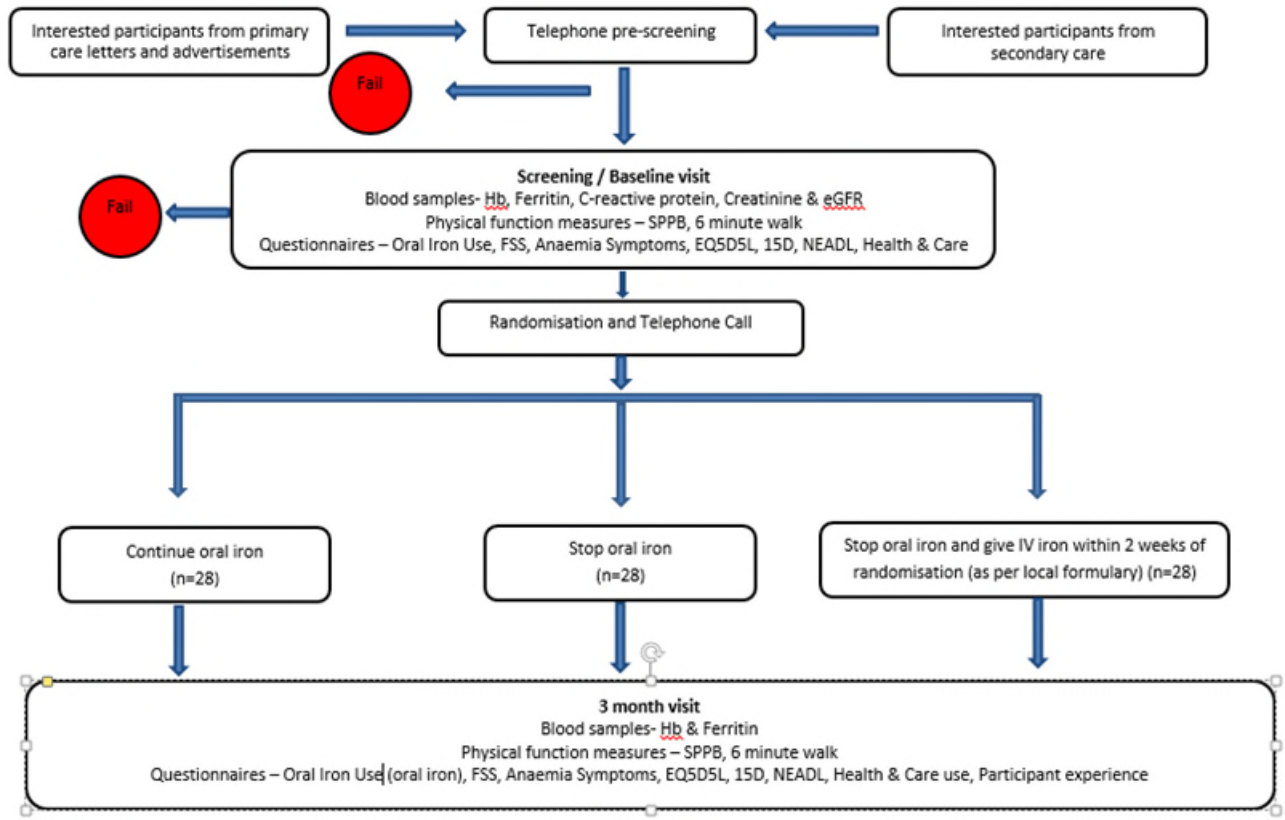
6) Dropout rate at 3 months
7) Crossover rate at 3 months
8) Change in functional limitation (six-minute walk <400m or short physical performance battery score ≤10) scores between baseline and 3 months
9) Change in level of fatigue assessed using validated Fatigue Severity Scale (19) between baseline and 3 months
10) Change in medication adherence using Oral Iron Use Likert scale (in those taking oral iron only) between baseline and 3 months
11) Participant experience using semi-qualitative questionnaire at 3 months.

3 STUDY DESIGN

3.1 STUDY DESCRIPTION

Three-arm, parallel group, open-label (assessor blinded) pilot randomised controlled trial.

3.2 STUDY FLOW CHART



Abbreviations
HB – Haemoglobin
EQ5D5L: EuroQol quality of life questionnaire
SPPB – Short physical performance battery
15D – health related quality of life questionnaire
FSS – Fatigue Severity Score
NEADL: Nottingham extended activities of daily living questionnaire.

Table 4: Study Matrix

	Visit 1 Combined screening and baseline visit	Visit 2 Randomisation and telephone call (+1 to 4 days)	Visit 3 IV iron administration visit (within 2 weeks of randomisation)	Visit 4 3 month visit (+/- 3 weeks)
Informed consent	X	X	X	X
Inclusion/Exclusion Criteria	X			
Demographics and medical history	X			
Adverse Events Recorded		X		X
Height and weight	X			
Medications	X			X
Oral Iron Use Scale	X			X[¶]
Haemoglobin	X			X
Ferritin	X			X
C-reactive protein	X			
Creatinine	X*			
eGFR	X*			
Short physical performance battery	X			X
Six-minute walk distance	X			X
Fatigue Severity Scale	X			X
Patient reported anaemia symptoms[&]	X			X
Quality of Life EQ-5D-5L & 15D questionnaires	X			X
Activities of Daily Living (Nottingham EADL score)	X			X
Health & Care Use questionnaire	X			X
Participants' experiences semi-qualitative questionnaire				X
Randomisation (telephone call)		X		
IV iron administration (if required)			X	
Nutritional advice leaflet				X

KEY

[X] Verbal consent check

* Screening creatinine and eGFR sample results will be within 12 months of study entry; if this is not available use baseline creatinine and eGFR results to determine eligibility.

[&] Complete at the end of Month 1 & 2; return at Month 3 visit.

[¶] Only participants randomised to continue oral iron – Telephone Call; unblinded RN.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Community dwelling people aged 65 years or over who meet the following study eligibility criteria and reside within the catchment area of participating NHS organisations. A total of 84 participants (approximately 21 in each NHS site i.e. 7 participants randomised into each study arm) will be recruited into the study.

4.2 INCLUSION CRITERIA

To be eligible, the participant will be assessed, and must meet all of the following criteria:

1. Provision of written informed consent
2. Community dwelling (i.e. not in hospital)
3. Age 65 years or over
4. Haemoglobin of >=85g/L and <=110g/L prior to commencing oral iron
5. Ferritin <100µg/L prior to commencing oral iron
6. Currently taking oral iron at any dose with a minimum of 8 weeks therapy
7. Insufficient response to oral iron therapy (sufficient response defined as improvement in Hb of 20g/L after a minimum of 8 weeks of oral iron therapy or above lower limit of normal Hb level for sex)
8. Relevant investigations (including upper and lower GI endoscopies) either already conducted, offered but declined by the patient, or deemed not appropriate by the treating clinician. Only if applicable:
9. Oral iron therapy provided an initial sufficient response however Hb has now fallen below lower limit of normal for sex (Sufficient response is defined as an improvement in Hb of 20g/L or Hb above lower limit of normal for sex after a minimum of 8 weeks of oral iron therapy).

4.3 EXCLUSION CRITERIA

To be eligible, the participant will be assessed, and none of the following criteria will be present:

1. Active GI cancers
2. Active (unhealed) peptic ulcer disease
3. No ferritin level performed prior to commencing oral iron
4. Bleeding disorders
5. Taking oral anticoagulants (antiplatelet agents are permitted)
6. Weight loss of >5Kg in the last 3 months (as a possible marker of occult cancer)
7. Estimated GFR of <30ml/min/1.73m^2 by CKD-EPI equation

8. Symptomatic chronic heart failure (NYHA (21) class III and IV); note asymptomatic left ventricular systolic or diastolic dysfunction is not classed as heart failure; the use of heart failure medications are permitted
9. Terminal illness with life expectancy less than 3 months as deemed by the local investigator
10. Severe cognitive impairment precluding written informed consent
11. Unable to mobilise without human assistance (walking aids are allowed)
12. Previous reaction to intravenous iron
13. Participating in another clinical trial (other than observational trials and registries) concurrently or within 30 days prior to screening for entry into this study.

5 PARTICIPANT SELECTION AND ENROLEMENT

5.1 IDENTIFYING PARTICIPANTS

5.1.1 Study sites

Participants will be recruited from four UK NHS sites: Grampian, Fife, Norfolk & Norwich, and Newcastle. The sites are selected as one large and one smaller site in both Scotland and England to establish the recruitment plan for the main study and to test whether these methods work in different geographical regions; for the main we anticipate increasing the number of sites, depending on the required sample size.

5.1.2 Channels of recruitment

Recruitment will target participants living in the community; in their own or another person's home, sheltered housing and care home (i.e. not in hospital).

Recruitment will target the following channels:

- Hospital clinics
- GP practice lists
- Laboratory results lists
- Research volunteer databases, including SHARE.

Recruitment strategies include (1) primary and secondary care oral iron prescriptions, (2) NHS electronic haematology records, (3) NHS clinicians and GPs identification of their patient lists (acute, outpatient and GP databases), (4) press release with associated recruitment materials such as posters displayed in hospital and GP surgeries (5) research volunteer database searches. Details are provided below (section 5.1.3).

Implementation will be through appropriate Research Ethics Committee, Caldicott Guardian and NHS R&D (22) consultants and GPs. For volunteers who contact directly to research team, we will check with their medical records regarding eligibility after their consent.

5.1.3 Recruitment Strategies

(i) Primary and secondary care prescriptions

To identify potentially eligible participants, oral iron prescription searches will be performed by Primary Care Network, GPs and/or hospital clinicians.

(ii) Laboratory results lists

To identify potentially eligible participants, biochemistry and haematology results listings will be created by the NHS laboratory at each site. Haemoglobin results will be reviewed by GPs/hospital clinicians or delegated.

(iii) Patient Lists

Hospital clinics

Potential participants will be identified by the clinical teams who look after the older patients (any speciality). Study protocol and eligibility criteria will be made known to all relevant clinical departments by the research team at participating sites; regular visits to these departments will be scheduled to ensure visibility and awareness of the study.

- Clinical teams will review patients receiving oral iron treatment to establish potential eligibility.
- The clinician will write to eligible participants using the Invitation Letter, providing the brief Participant Information Brochure, and inviting those interested in taking part to reply using the reply slip and stamped addressed envelope or to call or e-mail the study team.

GP Practice lists

Potential participants will be identified via the NHS Research Scotland Primary Care Network (NRSPCN) and NIHR Primary Care Network as follows:

- Research active general practices in the NRS / NIHR PCN will be invited to join the study.
  - **Recruitment of patients from the primary care by NRS & NIHR Primary Care Network**

The NRSPCN (previously called SPCRN) / NIHRPCN will be involved in recruitment of patients to this study from primary care. Network staff provide GP practices with an expert service to

undertake searches of their electronic databases to identify potentially eligible patients and prepare the ethically approved letters to be sent out by the practice. Network staff work on behalf of the healthcare team under practice staff supervision. Each member of Network staff must have a current NHS substantive or honorary contract in order to carry out these activities. Searches are undertaken of each GP practice database and the list generated by the search is screened by a clinician before the letters are sent out on behalf of the practice. Patients are asked to contact the research team if they are interested in participating in the study.

- Using the practice IT system and the Community Health Index (CHI) number (a unique NHS Scotland patient identifier) / relevant identifier a search of patients receiving oral iron treatment will be carried out to establish potential eligibility will be carried out to identify potentially eligible participants;.
- The GP will write to eligible patients using the Invitation Letter, providing the brief Participant Information Brochure, and inviting those interested in taking part to reply using the reply slip and stamped addressed envelope or to call or e-mail the study team.

(iv) Press release and advertising

Press and advertising in appropriate health care setting advertising will be utilised. The Sponsor will approve press release and/or advertisements. Interested individuals will contact the research team to request study information.

(v) Research volunteer databases

Relevant research volunteer database searches, including SHARE, will be employed to identify patients receiving oral iron treatment to identify potential participants. The research team will provide study information including a brief Participant Information Brochure, reply slip and pre-paid reply envelope.

5.1.4 Invitation Mailings

All invitation packs will be sent via HIC. HIC is a University of Dundee research support unit within the Tayside Medical Science Centre (TASC). All services provided by HIC are delivered within an ISO 270001 certified secure environment to ensure data is managed safely and in compliance with Data Protection legislation. The identified invitation lists will be stored securely within the NHS network. The invitation pack will consist of an invitation letter with a

reply slip, brief information sheet/leaflet and pre-paid return envelope. The research team will not have access to this confidential invitation list. HIC will also send any reminders with the relevant PIS.

Participants can indicate their interest in the study by completing and returning the reply slip using the pre-paid envelope or by calling/e-mailing the study team. Those interested will be sent information sheet. HIC will upload all positive replies allowing the relevant study team access contact details of the potential participant. These details are uploaded onto the secure web based Recruitment Tracker. The Cohort ID generated during the invitation stage will be used the participant identifier. For participants who state they do not wish to be contacted, their details will be not be uploaded and they will not receive any further communication. These details are not visible to the study team.

If required, a reminder letter will be sent to participants.

Participants who independently contact the study team having seen study information i.e. poster / advertising, the local team will upload the contact details onto the PMS, thereafter HIC will be send the invitation pack.

The Recruitment Tracker will document each positive response and with consent participant contact details allowing the study team to efficiently communicate with participants, GPs and secondary care physicians.

For data management purposes, identifiable information, completed consent forms and anonymised study data will be securely stored in locked cupboards, password protected databases and spreadsheets in the University of Dundee. Identifiable information will be stored separately from study data. Authorised members of the trial and data management team will have access to identifiable information to allow the management of study visits.

5.1.4.1 Managing Responses

- For all recruitment methods only the Personal Identifiable Data (PID) of potential participants' giving a positive response will be provided to the research team.

  NOTE: PID will be stored on the web-based electronic Patient Management System (PMS) hosted by Health Informatics Centre (HIC) (23). Secure access, via individual password protected accounts, will be provided to delegated research team members.

- RN or delegate will contact positive respondents via phone, email or letter (as per patient preference) to perform telephone pre-screening i.e. check inclusion and exclusion criteria. Those participants not noting any exclusion criteria will receive the full PIS (the RN will send by mail or email), be invited to attend a baseline visit and be given enough time to consider their participation. All questions will be answered fully before informed consent is obtained.
- Where no response is received to phone call / email after 3 attempts a reminder letter with a further PIS, reply slip and pre-paid reply envelope will be sent to the patient (to check their willingness to participate).

5.2 CONSENTING PARTICIPANTS

At the combined screening and baseline visit, written informed consent will be obtained by the local PI or delegate. The Delegation Log will detail staff (e.g. research nurses) who are appropriately qualified and trained staff and delegated to obtain informed consent. Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction. Normal capacity is presumed (initial judgement is made by clinical team performing pre-screening; in addition, the RN will liaise with PI if any doubt or concern is raised when the PIS is provided / screening visit booked), where there is concern the PI or medically qualified delegate will assess capacity prior to any informed consent discussion; severe cognitive impairment (in the opinion of the investigator) is an exclusion criterion. Informed consent will cover all study procedures. A copy of the signed Informed Consent Form along with a copy of the PIS will be given to the study participant. The original signed consent form will be retained at the study site and filed in the securely stored Investigator Site File (ISF) with an additional copy filed in the participant's medical notes.

Co-primary outcome data, including recruitment source will be provided via the PMS; this will be updated and Enrolment Log (filed within ISF) will be completed for all consented participants. Additional monthly Enrolment Log updates will be sent to the Trial Manager / delegate.

Eligibility and Informed Consent will be monitored as per the study Monitoring Plan

For participants recruited within NHS Fife specific written consent will be sought to link to routinely collected prescription, primary and secondary care use and social care data (see Section 0 and 0). This will be used to cross-validate information given by participants as preparatory work for using

such routinely collected data in a future large trial. The medication prescription data record linkage will be used as one of the measures to assess medication adherence.

A verbal consent check will be performed at each subsequent visit; recorded in participant medical record.

5.3 SCREEENING FOR ELIGIBILITY

Pre-screening and screening will be carried out by the RN or delegate; all inclusion and exclusion criteria will be checked as fully as possible.

All pre-screening and screening activity will be captured on the Screening Log (filed within ISF) and/or Excel Screening Activity spreadsheet: this co-primary outcome data will include number of patient notes reviewed; potential participants pre-screened and screened; reasons for ineligibility. Monthly Screening Log Excel spreadsheet updates will be sent to the Trial Manager / delegate. No PID will be provided to the study team.

The combined screening and baseline visit will take place at a local clinic or research facility, depending on where is most convenient for participants in each area.

The final eligibility check will be performed at the combined screening/baseline visit and prior to randomisation all inclusion and exclusion criteria will be confirmed by the PI/medically qualified delegate. This signed eligibility confirmation will be recorded in the Case Report Form (CRF) and medical notes.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Screening data will be retained for participants that are not subsequently randomised; this will not contain PID. The reason(s) for ineligibility will be:

- Logged on the study Screening Log
- Explained to the participant and any questions they have will be answered.
- Ineligible participants will be thanked for their interest; any relevant clinical information will be added to their hospital notes and communicated to their GP (with consent) and reassured that by withdrawing from the study this will not affect their future medical care. Rescreening, previously ineligible participants, will not occur in this pilot study.

5.5 RANDOMISATION

5.5.1 Randomisation

After successful screening for eligibility and safety, and completion of baseline outcome measures, participants will be randomised on a 1:1:1 allocation ratio via a web-based system TRuST, run by the Tayside Clinical Trials Unit (TCTU) and hosted by HIC, to preserve allocation concealment. The TRuST system will be based on the study protocol; system validation and User Acceptance Testing will follow HIC and TASC SOPs; CI review and approval will be carried out prior to the live system release.

The study arms are:

- Continue oral iron
- Stop oral iron
- Stop oral iron and give IV iron (as per local formulary).

Direct care physicians (i.e. GP or hospital clinician) will receive written notification of the randomisation allocation. Participants will be verbally informed of treatment allocation (telephone visit). Treatment allocation will be recorded in the participant medical record.

Where web-access is not possible at site, emergency randomisation will be provided by TCTU via telephone 01382 383581; following the TCTU Unblinding Work Instruction. Verbal notification of randomisation will be provided; email record of emergency randomisation will be provided when web-access is available) and filed in the participant medical record.

A minimisation algorithm with a random element will be used to ensure balance across recruitment centres and key baseline measures. Randomisation will be stratified by site, and further balanced using minimisation. Haemoglobin after minimum 8 weeks of oral iron (>=100g/L vs <100g/L), ferritin prior to commencement of oral iron (>=50ug/L vs <50ug/L) and six minute walk distance (>=300m vs <300m) will be the minimisation variables.

Only those involved with development and maintenance of the system will have access to the treatment allocations during the study; those involved with outcome assessment or statistical analysis will not have access to allocation until the point of the final analysis after database lock. Unblinding will occur following OC database lock; the CI will formally request unblinding.

5.5.2 Withdrawal procedures

Participants will be withdrawn from the study if a) they request to withdraw, or b) they lose capacity to give informed consent (as assessed by the clinical judgement of the local PI/delegate). Withdrawal will be as per Sponsor SOP and documented using the Sponsor Withdrawal Form.

Any physician, involved in direct care (i.e. GP or hospital clinician) or study care (i.e. PI/ medically qualified delegate), using their clinical judgement may withdraw a study participant from their randomised treatment. This may occur due to the occurrence of:

- an adverse event (AE)
- the onset of a symptom that is deemed related to the study participation or related procedures
- the onset of a symptom that is an exclusion criteria
- any other reason which in their clinical judgement requires the participant to be withdrawn

Patients withdrawn from randomised treatment will remain in the study (with consent) for safety follow-up and outcome measures, and will be included in the intention to treat analysis (ITT) but will be censored in per-protocol analyses. If withdrawal is due to a study intervention product related AE it will be logged as such on the Adverse Event Log. All reasons for withdrawal will be noted in the participant's CRF and medical notes.

If at any time the participant formally withdraws his/her consent for future participation and disclosure of future information, no further evaluations will be performed and no additional data will be collected. With consent, data collected before withdrawal will be retained and used in the study analysis; where withdrawal includes data, and if this occur before data base lock, the data will be excluded from analysis. Although a participant is not obliged to give reason(s) for withdrawing consent prematurely, if the participant appears lost to follow up, the CI will make a reasonable effort to ascertain the reason(s), while fully respecting the individual's rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

A dropout rate of 30% is assumed, we therefore aim to recruit and randomise up to 84 participants to ensure that we have 20 completed participants per treatment arm (60 in total).

6 INVESTIGATIONAL PRODUCT

Note: This study is a non-CTIMP.

6.1 ACTIVE INVESTIGATIONAL PRODUCT

The study compares three strategies of care: withdrawal of oral iron, continuation of oral iron, or switching from oral iron to intravenous Iron. All these drugs are normally used in the NHS to treat iron deficiency anaemia. The study does not compare the safety or efficacy of these iron preparations.

- Oral iron has been previously prescribed by the direct care physician (i.e. GP or hospital clinician).
    - At randomisation continuation or discontinuation will be notified in writing to the direct care physician and verbally (via telephone visit).
- IV Iron will be prescribed by the site PI or delegated medically qualified research team member.
    - Local policies will apply.
    - Ferric carboxymaltose or iron sucrose will be permitted, this reflects current clinical practice where different sites use different preparations.
    - The dose and administration time of IV iron will be calculated using both the participant's bodyweight and the haemoglobin level. This is in line with current prescribing practice.
    - NHS emergency/resuscitation facilities are available at each study site.
    - In a suitable clinical setting the participant will receive IV iron infusion according to local policies for the safe administration of IV iron.

6.2 STUDY INVESTIGATIONAL PRODUCT STORAGE

Oral and IV iron preparations will be purchased and stored within Pharmacy as per product storage information and as per local Pharmacy guidelines. The quality assurance of storage conditions will be as per local Pharmacy procedures.

6.3 STUDY INVESTIGATIONAL PRODUCT REFERENCE SAFETY INFORMATION

Summary of Product Characteristics (SmPC) will be as per locally used oral and IV iron preparations.

The potential side effects of IV iron will be communicated to participants in writing via the PIS and verbally during informed consent discussion.

The current copies of the SmPC for the oral and IV iron preparations in use at site, will be filed in the ISF for the purpose of detecting any potential Adverse Drug Reaction (ADR) related to IV iron therapy.

The PI is responsible for ensuring that:

- The research team has easy access to the SmPC.

  NOTE: The PI / medically qualified and delegated individual will be responsible for assessing severity and causality for any and all potential Adverse Drug Reactions.
- Oral and/or IV iron preparation changes are communicated to the CI/ delegated Trial Manager.

6.4 ACCOUNTABILITY PROCEDURES

No study drug accountability will be required.

- IV iron accountability will supervised by the NHS Pharmacist at each study site and as per local NHS Pharmacy prescribing, dispensing and drug administration policy.
- Oral iron accountability will be supervised by a Pharmacist and as per local prescribing, dispensing and drug administration policy.

7 STUDY ASSESSMENTS

7.1 OUTCOME ASSESSMENTS

At each site study assessments (baseline and follow-up outcome assessments) will be carried out by a Research Nurse (RN), or other appropriately trained and delegated individual. The follow-up assessment will be carried out by a blinded RN. This is required to maintain treatment allocation blinding: i.e. the outcome assessments must be collected by a different blinded RN, and not the individual undertaking randomisation. Where this is not possible a deviation will be recorded on the study Deviation Log.

- Assessments are scheduled as per the Study Matrix (Table 4); additional instruction is provided via the Operations Manual.
- All study data will be reported using the study CRF; entered into OC.

- The PMS will be used to track and manage participant study visits; access will be restricted to delegated members of the research team.
- Visits will be recorded in the patient medical record, including all trial data relevant to a participant's general medical history.

7.1.1 Screening and Baseline Visit

See Study Matrix (Table 4).

At screening/baseline the following will be collected from participants and their medical notes:

- Inclusion / exclusion criteria check
- Demographic information including home circumstances and use of mobility aids
- Medical history and medication review
- Height and weight

Additionally the following will be performed:

- 10ml of non-fasted blood will be taken for local laboratory haematological and biochemical analysis:
    - Haemoglobin, ferritin, c-reactive protein, creatinine and estimated GFR (using CKI-EPI equation)

  Local laboratory ranges will apply.

  Samples taken at this visit are baseline samples and the results are NOT required to determine eligibility:

    - Eligibility assessment requires haemoglobin and ferritin results from before oral iron treatment started and haemoglobin level after a minimum of 8 weeks of oral iron therapy.
    - C-reactive protein baseline samples will NOT be used to determine eligibility.
    - Screening creatinine and eGFR sample results will be within 12 months of study entry; if this is not available baseline creatinine and eGFR results will be used to determine eligibility.
- Assessment of Physical function is carried out using the following widely used standardised clinical tests of walking speed, static and dynamic balance abilities:
    - Short Physical Performance Battery (SPPB) (15). This group of measures combines the results of the gait speed, chair stand and balance tests.
    - Six-minute Walk Test. This provides walking speed.

  Details of the procedures and equipment used for these tests of physical function will be provided in the study Operations Manual.

- Health and social activity will be collected using the following self-reported questionnaire data collection tools (non-validated tools are provided as appendices):
  - Oral Iron Use Scale – self-reported, Likert scale (Appendix 2).
  - Fatigue Severity Score (19) – self-reported, validated tool
  - Patient Reported Anaemia Symptoms – self-reported scoring at the baseline and the end of each month (Appendix 1).
  - EQ5D-5L (quality of life) (16) – self-reported, validated tool.
  - 15D (health related quality of life) (20)– self-reported, validated tool.
  - NEADL score (activities of daily living) (18) – self-reported, validated tool to assess and score physical function.
  - Health & Care Use - self-reported health care utilisation semi-qualitative questionnaire (Appendix 3).

7.1.2 Telephone Visit

Following randomisation, which is completed by the unblinded research team member, the telephone visit will be performed by the delegated unblinded research team member to inform the participant of treatment allocations.

For participants randomised to receive the iron infusion, the delegated unblinded research team member will contact the relevant NHS team to schedule the visit.

The unblinded research team member will send the Recruited GP Letter to advise GP of treatment allocation.

NOTE: Randomisation will be completed by a different (unblinded) member of the research team, and not the research nurse who will carry out the follow-up visit; this will assure blinded assessment.

7.1.3 Iron Infusion Visit

IV iron administration is a routine procedure in the NHS. Local policies and procedures will apply.

The infusion will be administered by a Registered Nurse / appropriately qualified member of the NHS team. The research team will remain blinded to treatment allocation.

The unblinded RN or delegate will attend the infusion visit.

7.1.4 Follow-up Outcome Assessment Visit

See study matrix (Table 4)

The following will be performed by the blinded RN at the outcome assessment visit:

- 5ml of non-fasted blood will be taken for local laboratory haematological and biochemical analysis:
  - Haemoglobin and Ferritin
- Assessment of Physical function:
  - Timed up and Go Test (TUG).
  - Short Physical Performance Battery (SPPB)(15).
  - Six-minute Walk Test.

  Details of the procedures and equipment used for these tests of physical function will be provided in the study Operations Manual.
- Health and social activity will be collected using the following self-reported questionnaire data collection tools (non-validated tools are provided as appendices):
  - Fatigue Severity Score (19)
  - Patient Reported Anaemia Symptoms
  - EQ5D5L (quality of life) (16, 17)
  - 15D (health related quality of life) (20)
  - NEADL score (activities of daily living) (18)
  - Health & Care Use
  - Participant experience and views (Appendix 4)

For participants randomised to receive oral iron the unblinded RN will telephone the participant to complete the Oral Iron Use Likert Scale.

After study assessments have been carried out, and to preserve blinding, the following will be collected from participants and their medical notes:

- Adverse events
- Medication review.

Participants will be provided with iron specific dietary advice (24) at the end of the Follow-up visit.

At the end of study participation the GP will resume care and iron prescribing; additionally:
- the RN will direct the participant to contact their GP
- the GP will be directed (via GP letter – recruited) to review Visit 4 Hb and ferritin results.

7.2 SAFETY ASSESSMENTS

Adverse events will be collected at visit 2 and 4 by direct questioning of participants regarding health and social care contacts, hospitalisations and new symptoms. Details of current medication will be collected at visit 4. The participant's hospital medical record will be reviewed at visit 4; details of all AEs and concomitant medicines will be collected and recorded.

NOTE: Where a discrepancy is identified between participant and medical record reported AE / concomitant medication the PI, or medically trained delegate, will clarify and define the data to report; this decision will be recorded in the medical record.

AEs and concomitant medications are not collected at Visit 3 for the IV iron treatment group; the scientific justification for not collecting this data at Visit 3 is to prevent skewed/over- reporting due to additional data collection.

Where possible to investigators should remain blinded to treatment allocation.

The PI / medically qualified and delegated individual will be responsible for assessing severity and causality for any and all AEs and potential ADRs. Section 4.8 of the relevant SmPC will be used as reference safety information for the assessment of ARDs.

NOTE: SmPC will be as per locally used oral and IV iron preparations.

8 DATA COLLECTION & MANAGEMENT

8.1 DATA COLLECTION

It is the CI's responsibility to ensure the accuracy of all data entered and recorded in the CRFs, the database and spreadsheets. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry and discrepancy management.

The paper CRF, designed by TCTU and approved by the CI, Statistician and Health Economist, will be issued to sites following site activation. Competed CRFs will be stored in a secure, restricted access storage facility.

The data will be collected by the RN, or other delegated person and/or the Site PI and entered into a paper CRF. Information will then be transferred contemporaneously (and within a maximum of 10 working days), by delegated staff, to the web-based study electronic database run in OpenClinica or

the PMS hosted by HIC. Delegated staff will carry out visual verification of data entered from CRF to OC; this quality control activity will be logged and a copy provided to the trial manager / delegate for review. All research data and data established from the NHS tests will be stored in an unidentifiable format on this secure, password protected database hosted by HIC, University of Dundee.

The PMS will be updated by delegated staff; this will provide co-primary outcome recruitment data. Screening activity will be entered onto the Screening Activity Excel spreadsheet; this will be updated and provided each month to the Trial Manager / delegate.

To preserve blinding the follow-up Oral Iron Use Scale (oral iron only), iron treatment and Participant Experience and Views questionnaires will be quarantined. The unblinded RN will transfer the Oral Iron Use Scale and iron treatment data onto version controlled Excel spreadsheets. LabKey will be used to securely upload the Excel Oral Iron Use Scale and iron treatment data files and Participant Experience questionnaires. Following data lock these data will be analysed separately from the main dataset; by the Health Economics Research Unit (HERU) based in the University of Aberdeen.

The medical notes or electronic health records will provide source data for past medical history, prescriptions, subsequent medical conditions, hospital admissions, diagnostic reports and blood results.

NOTE: To preserve blinding, the blinded RN should avoid reviewing the medical record until follow-up outcome assessments have been completed.

The CRF and study questionnaires will be used as source data, where appropriate, and data relevant to a participant's general medical history will also be recorded in their case notes.

Following database lock HIC will perform NHS data linkage for the Fife site only, for cross-validation purposes. Established over 10 years ago, HIC is recognized as a leader in health data linkage (25), and were the first centre in Scotland to offer a Safe Haven, this is Nationally Accredited and ISO27001 certified. Operating under tight data governance controls, the Safe Haven allows secure collaborative research using sensitive eHealth data.

HIC maintains a clinical data repository of eHealth data covering approximately 20% of the Scottish population. The eHealth repository combines routine collected datasets for the Tayside and Fife population and Tayside, with local speciality research, and clinical datasets. All HIC's clinical datasets are fully indexed and electronically linkable.

The following routinely collected NHS data will be obtained:

- medication prescription data to assess medication adherence
- hospital record (SMR 00 Outpatients; SMR01 Inpatients and Day Cases) and GP attendance data to assess health care use.

These data will be pseudo-anonymised as per HIC SOPs.

The cross-validation dataset will be securely accessed via the HIC Safehaven. This data will be provided within a separate file, and not imported into the OpenClinica database.

Statistical modelling will be used for other sites.

8.2 DATA MANAGEMENT SYSTEM

The web-based PMS / recruitment tracker hosted by HIC, University of Dundee, will be designed to capture and report the co-primary outcomes. Formal / documented User Acceptance Testing will be carried out by TCTU prior to the CI conducting a review and system approval (prior to release of the live system).

The web-based data management system, OpenClinica (OC), will be provided and managed by TCTU, University of Dundee using a GCP compliant system. The Screening Activity and Oral Iron Use Scale (oral iron only) and iron treatment Excel spreadsheets will be created and provided by TCTU. OC and the Excel Oral Iron Use Scale and iron treatment databases will be based on the protocol and the CRF. All databases will be subject to formal / documented User Acceptance Testing and the CI / delegate will conduct a review to ensure that OC database, the Excel Oral Iron Use Scale and iron treatment spreadsheets match the CRF; prior to release of the live OC database and Excel spreadsheets the CI will approve the systems. OC database and Excel spreadsheet version changes will be managed as per TASC SOPs. The CRF, OC and Excel spreadsheets will not collect more information than is required to meet the aims of the study and to provide evidence of eligibility and safety of the participant.

The NHS Fife prescribing and health and social care use data (for data linkage) will be obtained and processed by HIC following OC database lock. This will be stored within a separate database on the NHS Tayside Safehaven.

Any queries will be resolved by the Investigator or delegated member of the study team. TCTU will generate and issue data query forms; following source data review sites will provide response,

update CRF and OC. Queries will be issued to sites throughout the study, with the aim of completing database lock within 3 months of the last patient last visit.

Password protected access and use of PMS, OC, data spreadsheets and Safehaven will be restricted to relevant research team members; will be granted for study monitoring purposes.

Development and validation of the study database and QC and extraction of data will be carried out according to TASC procedures and SOPs; records of these activities will be filed within the Data Management section of the TMF. Extracts for analysis will be managed by TCTU and based on the Statistical Analysis Plan (SAP).

The Data Management Plan and SOPs will provide details of the system and processes.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Since this is a pilot study, under CSO guidance, no formal sample size calculation is provided – indeed this pilot study will furnish indicative data to allow a sample size calculation for the full trial. We will aim to have 20 completed participants in each arm (60 in total). The target is set at 20 completed participants per arm so as to have sufficient variability in response to provide estimates for future sample size calculation. We also would like to have a sufficient number to examine the feasibility of the recruitment pathways we are proposing. It is also in line with current practice in which a pilot study sample size is ~40-50 for a two-arm trial. Assuming a dropout rate of 30%, we therefore plan to recruit and randomise a total of 84 participants. We will recruit for a maximum of 15 months at four sites (total target N=84).

Linked NHS Fife prescribing and health and social care use data will used for statistical modelling; this will use data from a maximum of 21 participants. Our aim is to test the process of obtaining linked data and to conduct preliminary data verification to inform the main study; to obtain standard deviation and mean outcome variables and to calculate the sample size for the main study and not to obtain statistical results of significance.

9.2 STATISTICAL ANALYSIS PLAN

All analyses will be by intention to treat, and will thus include all participants randomised. Data will be analysed by an independent statistician from Medical Statistics Team and a Research Assistant from HERU.

Baseline demographics and clinical characteristics will be presented as mean (SD), median (IQR) or percentage (n) as appropriate across study arms. Hb and ferritin level at 3 months will be compared across study arms using analysis of covariance with baseline Hb and ferritin level and site as covariates. Intra study arm comparisons will be assessed using the paired t-test or Wilcoxon signed rank test. Number of eligible patients per site, recruitment rate across sites, the proportions recruited by each method within site, dropout and crossover rates, all with corresponding 95% confidence intervals will each be tabulated. Effect size estimates of difference in Hb and ferritin level between arms will be calculated. The latest available SPSS version at the time of conducting statistical analysis will be used for analysis with intention to treat as the main analysis.

A per-protocol analysis will also be performed on completers of the study as a secondary analysis, primarily for safety outcomes (adverse event rates, falls).

Health economic measures (costs of healthcare use, comprising hospital stays for reasons related to

anaemia and outpatient/day case visits for iv iron administration, costs of blood transfusion and oral iron, and quality of life measurement using EQ-5D-5L and 15D) will be presented as unadjusted mean (SD) and median (IQR) values. Regression-based adjusted costs and quality of life values will also be calculated, with baseline cost, quality of life values, treatment group and patient demographics as co-variates. The percentage of missing data per resource use item and per quality of life questionnaire will also be presented.

We will assess both feasibility of secondary outcome measures and distribution of changes; these data will form the basis for sample size calculations for the full trial.

Experience and tolerability from a patient perspective will be assessed by the participant experience questionnaire, completed at the follow-up visit by all participants. The semi-quantitative data will be analysed using SPSS and presented descriptively whilst free text data will be transcribed verbatim to excel spread sheet to derive themes using thematic analysis approach. Semi-qualitative data that are not part of the OpenClinica study database will be analysed via their unique study identifier.

9.3 TRANSFER OF DATA

Data transfer from sites to TCTU and from TCTU and HIC to Sponsor Institution/co-investigators (e.g. HERA) will be via LabKey, a secure data transfer server facility provided by TCTU.

Data will be retained for at least 15 years. Archiving and destruction will be as per Sponsor SOP.

10 SAFETY ASSESSMENTS

As the study is defined as a non-Clinical Trial of Investigational Medicinal Product, Adverse Events (AE) and Serious Adverse Events (SAE) not defined on the exception list (see Section 10.1.1) will be recorded and reported as per Health Heath Research Authority (HRA) and Sponsor's guidelines for non-CTIMP reporting (summarised in Table 5**Error! Reference source not found.**).

A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. However, any adverse events occurring during such hospitalisation will be recorded. See section 10.1.1 for further AE and SAE reporting exemptions.

10.1 RECORDING AND REPORTING AEs AND SAEs

AEs and SAEs will be recorded from the time of written informed consent until the last study visit.

- Only AEs which have resulted in the participant seeking advice or treatment from a healthcare professional will be recorded.
- The PI or delegate will ask about the occurrence of AEs and hospitalisations visits 2 and 4 only.
- Once the Investigator becomes aware that an AE or SAE has occurred in a study participant, they must enter the information into the CRF AE Log and entered (in a timely fashion) into the OpenClinica database.

- Participants with unresolved AEs at the last study visit will be followed up until resolution or 30 days after their last study visit, whichever is sooner.

An SAE occurring to a research participant will only be reported as per HRA guidelines to the main REC, and copied to the Sponsor (as per University of Aberdeen SOP) via pharmaco@abdn.ac.uk, where in the opinion of the Chief Investigator the event was:

Related – that is, it resulted from administration of any of the research procedures, **and**

Unexpected – that is, the type of event is not listed in the protocol or Reference Safety Information (section 6.3) as an expected occurrence.

unless meeting a AE/SAE reporting exception category, as outlined in section 10.1.1 (below).

Table 5: Safety Reporting

	Who	When	How	To whom
SAE	Chief Investigator (CI)	Within 15 days of the CI becoming aware of the event	SAE report form for non-CTIMPs	Main REC for the study.
Urgent safety measures	Chief Investigator (CI) or sponsor *Or exceptionally by local principal investigator (PI)*	(i) Immediately (ii) Within 3 days	(i) By telephone (ii) Notice in writing setting out the reasons for urgent safety measures and the plan for further action	Main REC: study co-ordinator will acknowledge within 30 days

Reconciliation of SAEs (reported to Sponsor as per SOP) will be carried out by the TCTU Data Management Team; the Sponsor representative will provide the reported SAEs to TCTU.

All AEs will be MedDRA (26) coded by the TCTU Data Management Team.

10.1.1 AE & SAE Exception List

Due to the large amount of comorbid disease and very high levels of illness and adverse events that we expect to be present in this population, we will record all Adverse Events but not report to REC those classified as SAEs, in the following categories:

- Any death or hospitalisation due to a new cardiovascular event
- Any death or hospitalisation due to new diagnosis or treatment of cancer

- Any death or hospitalisation due to exacerbation of an existing medical condition
- Any admission for elective or planned investigation or treatment
- Any death or hospitalisation due to nausea, vomiting, constipation or diarrhoea
- Any death or hospitalisation due to a fall.

10.2 REGULATORY REPORTING REQUIREMENTS

The CI will inform Sponsor & REC within 15 days of any reportable SAE or Urgent Safety Measure; as per HRA guidelines for Non-CTIMP safety reporting (summarised in Table 5**Error! Reference source not found.**).

10.3 ANNUAL REPORTING REQUIREMENTS

The following reports will be submitted each year as a condition of the authorisation to undertake a clinical trial or as a condition of a favourable opinion from a REC:

- NRES Annual Progress Report will be prepared and submitted by the CI to REC, and copied to Sponsor, on the anniversary date of the REC favourable opinion.
- NRES Safety Report Form will be sent to the REC. This will provide details of causally related SAEs (occurring in the UK), Urgent Safety Measures and any other safety reports submitted (for example: Data Monitoring Committee reports).
- These reports will be copied to the Sponsor.

10.4 URGENT SAFETY MEASURES

The CI or other clinician may take appropriate immediate urgent safety measures in order to protect the participants of the study against any immediate hazard to their health or safety. The REC and Sponsor will be notified in writing within three days.

11 PREGNANCY

The target population are of an age to preclude pregnancy

12 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP (TMG)

The study will be coordinated by a Trial Management Group, consisting of Chief Investigator, Principal Investigators, and key grant holders, study co-ordinator and relevant TCTU staff.

12.2 TRIAL MANAGEMENT/COORDINATION

A Study Coordinator will be based at the Sponsor site, and will liaise closely with the TCTU Trial Manager. The Trial Manager will form the central point of coordination for the study, with oversight and guidance given by a senior staff member at TCTU; all three will be accountable to the Chief Investigator.

A Delegation Log will be prepared for each site, detailing the role of each member of staff working on the study. The PI is responsible for maintaining the Delegation Log. Copies of the Delegation Log, study specific training records (Site Initiation Training attendance record, SOP reading log, Operations Manual confirmation of reading, electronic systems certificates of training), signed Curriculum Vitae and Good Clinical Practice certificates (including updates) will be provided to the Trial Manager / delegate for review to ensure that all staff are appropriately qualified and trained for their delegated role. Regular communication, including teleconferences, will ensure that site staff share best practice. Refresher training will be provided by the trial manager where no study activity has been undertaken for a period of 3 months or more.

12.3 DATA MONITORING

An independent data monitor, Dr Terrence Quinn (Senior Clinical Lecturer) will review the study protocol and CRF prior to study commencement and report on final study data, provided by the study statistician, at the end of the study; and if/as requested by the study funder. In addition the Statistical and Health Economic Analysis Plans will be reviewed by the independent data monitor. A charter containing details of role, reporting and accountability for the independent data monitor will be produced prior to the commencement of the study.

12.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study risk assessment was carried out by the Research Governance Manager of the Sponsor prior to Sponsorship approval being granted.

12.6 STUDY MONITORING

The Sponsor will determine the appropriate extent and nature of monitoring for the study and will appoint appropriately qualified and trained monitors if required. Any monitoring will be provided within the Monitoring Plan. For monitoring purposes the Source Data Identification list, generated by the Trial Manager / delegate and secure, password protected access to TRuST, OC and Excel spreadsheets will be provided.

12.6.1 Potential Risks

- Risks associated with invitation to participate:

Potential participants may not be aware that their oral iron supplementation has not improved their anaemia. To avoid causing concern, and any potential adverse impact for the GP-Patient relationship, text relating to suboptimal response has been avoided in the participant information and invitation letters.

- Risks associated with study outcome procedures:

Venepuncture carries the risk of bruising and discomfort, but will be undertaken by experienced staff with access to additional staff if required.

Study visits potentially can lead to fatigue due to travel and attendance. All participants will have access to taxi transport and will be given time to rest between each study assessment. Participants will be able to rest after each visit, and will be offered refreshments.

Close monitoring of patients in the study has the potential to uncover new diagnoses or clinically important findings. The PI will communicate to the participant's GP, in writing, any relevant incidental findings with participant's consent.

- Risks associated with medication used in treatment strategies:

These include known side effects of oral and IV iron, drug hypersensitivity reaction, and idiosyncratic reaction. All sites which will deliver the IV iron medication have facilities to deal with any acute reactions including to severe anaphylaxis and cardio-respiratory arrest situation. Any signs or

indications of potential side effects during IV therapy will be monitored closely by the Nurse who will be present with the participant throughout the IV administration.

12.6.2 Minimising Risk

All associated risks for both oral and intravenous iron use are well understood and have established procedures for management as part of their use in routine NHS care where the treatments will be delivered.

Participants will receive contact and emergency contact details in PIS and via a Participant Study Card. These study staff contact details will enable patients to contact staff with any concerns and to allow the study team to support participants in the event of any adverse event that cannot be dealt with via usual NHS services.

All patients will have access to taxi transport for each visit to aid accessibility, convenience and retention. Travel costs will be reimbursed.

Risks of venepuncture will be discussed and undertaken by experienced staff with access to additional staff if required.

The screening process will reduce risk by excluding those people where study procedures/intervention would interfere with current best medical practice in managing any comorbid disease.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP) and the UK Policy Framework for Health and Social Research (22). In addition to Sponsorship approval, a favorable ethical opinion will be obtained from an appropriate REC and appropriate NHS R&D permissions will be obtained prior to commencement of the study.

13.1.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written

permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee or Regulatory Authorities.

The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

13.1.2 Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 and subsequent update to General Data Protection Regulations, with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland & England Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13.1.2 Insurance and Indemnity

The University of Aberdeen and NHS Grampian are Co-Sponsoring the study.

Insurance: select the applicable text form the list below:

- University of Aberdeen will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.
- Grampian Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Grampian in relation to the study.
- Where the study involves University of Aberdeen staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Grampian Health Board which means they will have cover under Grampian's membership of the CNORIS scheme.

Indemnity: The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

The CI will seek Sponsor approval for any amendments to the Protocol or other study documents. Amendments to the protocol or other study docs will not be implemented without approval from the Sponsor and subsequent approval of substantial amendments from the appropriate REC and NHS R&D Offices.

14.2 PROTOCOL DEVIATIONS, BREACHES AND WAIVERS

The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to study participants.

In the event that the CI/PI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented in the study Deviation Log and notified to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and local NHS R&D for review and approvals as appropriate. It is Sponsor policy that waivers to the Protocol will not be approved.

In the event that a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the form Notification to Sponsor of Potential Serious Breach of Good Clinical Practice (GCP) or Study Protocol.

14.3 STUDY RECORD RETENTION

Archiving of study documents and electronic data will be carried out as per SOPs of the Sponsor. All study documentation and electronic data will be kept for at least 15 years. TCTU will provide the TMF and electronic study data, via Sponsor approved (and funded) courier transfer; this will be stored on behalf of the CI within the Data Safe Haven (DASH), University of Aberdeen. ISFs and CRFs will be archived locally at sites, the Archive Approval Form (TMP QA 34) will be completed by sites and provided to the Study Coordinator / delegate for inclusion with the TMF archive. At the end of the archiving period destruction will be carried out as per Sponsor SOP.

14.4 END OF STUDY

The end of study is defined as database lock. The Sponsor or CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor, REC, and NHS R&D Office(s) within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A final report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

Main study results will be posted to a publicly-available Clinical Trials Registry (ISRCTN) within 1 year of the end of the study.

14.5 CONTINUATION OF TREATMENT STRATEGY FOLLOWING THE END OF THE STUDY

The participants will be able to make informed decision (based on their study experience) and discuss with their GPs for their preferred treatment option. This empowers patients to use autonomy and promote shared-decision making.

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

15.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Study investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

15.3 PEER REVIEW

The grant proposal for this study has been subjected to external peer review via the Chief Scientist Office, Scottish Government - the funding body.

15.4 DATA SHARING

At the end of the study, study data will be archived; pseudo-anonymised study data will be made available on request to other bona fide academic investigators via data sharing agreements overseen by the University of Aberdeen.

15.5 DISSEMINATION PLAN

Results will be disseminated through public engagement activities led by the study team with support from the Public Engagement in Research Unit (PERU) of the University of Aberdeen with input from our lay service users. In particular we will be taking advantage of the internationally-excellent programme which Aberdeen has in engaging with members of the public in research: http://www.abdn.ac.uk/engage. Our dissemination activities will also benefit from the Service Users' Groups, locally established networks of volunteer members of the public who actively wish to contribute in research by working alongside the researchers in delivering successful research studies and disseminating to wide ranging beneficiaries including patients, public, health care providers, commissioners and policy makers. We also have extensive Cafe series in University of Aberdeen- *CafeMed*, http://www.abdn.ac.uk/news/9087, *Cafe Scientifique* and *May Festival* - as public engagement mechanisms and such programmes provide excellent opportunities to the researchers for public engagement.

Through our respective communication departments, we will advertise the study widely to the public through press and media from funding stage to dissemination of results. At the end of the study, we will invite participants and family members to attend a tea party (at each site) to share the results with them and receive their formal (written feedback on a feedback form) and informal feedback (through conversation with the research team members) on how the study went, and ways to improve future study design.

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APPENDIX 1: PARTICIPANT REPORTED SYMPTOMS

Participant ID:							Date:							
							D	D	-	M	M	-	Y	Y

Baseline Participant Reported Symptoms

Over the last week, how much have the following symptoms affected you?

Symptom	Not at all	A little	Somewhat	Quite a lot	A great deal
Feeling tired					
Being out of breath when I walk					
Being out of breath when I am at rest					
Feeling dizzy or lightheaded					
Having a sore tongue					
Having restless legs during sleep					
Having cramps in my legs at night					

RAINDroP Baseline Participant Reported Symptoms Version 1 10/01/18
IRAS Number: 233417

APPENDIX 2: ORAL IRON USE SCALE

Baseline Oral Iron Use (Self-report)

Please read each statement then tick or circle one response

Since starting oral iron (tablets or medicine)

1. I have forgotten to take it

Very Often	Often	Sometimes	Rarely	Never

2. I take it at the same time every day

Always	Usually	Sometimes	Rarely	Never

3. When I feel better I stop taking it

Always	Usually	Sometimes	Rarely	Never

4. When I feel worse I stop taking it

Always	Usually	Sometimes	Rarely	Never

RAINDroP Baseline Oral Iron Use Version 1 14/06/18
IRAS Number: 233417

APPENDIX 3: CARE USE QUESTIONNAIRE

Participant ID:							Date:								
							D	D	-	M	M	-	Y	Y

RAINDroP: RAndomised IroN Deficiency anaemia management Pilot

Care Use Questionnaire

These questions help us to understand your use of health and social services because of your iron deficiency anaemia.

Iron deficiency anaemia

Some people with iron deficiency anaemia do not notice any problems or limitations. Other people notice problems, which may include:

- tiredness and lack of energy (lethargy)
- shortness of breath
- noticeable heartbeats (heart palpitations)
- a pale complexion.

More information is available from the study team, your doctor or the following website:
https://www.nhsinform.scot/illnesses-and-conditions/nutritional/iron-deficiency-anaemia

Please read the questions carefully and write your answers in the spaces provided. If you cannot remember things exactly please give your best estimate. Feel free to add any of your own notes.

Participant ID:					

Hospital visits

1. a) Thinking back **over the past three months**, how many times have you been into **hospital because of your anaemia?**

	Number of visits	Reason for visit/s
For outpatient appointment		
For daycase appointment (for example: to see a doctor or to have a procedure carried out; no overnight stay)		
Overnight hospital stay		

b) If you had an overnight hospital stay, how many nights did you stay?
Please tell us for each stay:
Stay 1 _____ Stay 2 _____ Stay 3 _____ Stay 4 _____

c) If you had a hospital visit or overnight stay, did you receive any of the following?
(Please tick either yes or no)

	Yes	No
Iron "infusion" with a needle		
Iron tablets or medicine		
Blood transfusion		

Participant ID:					

Community health services

2. Thinking back **over the past three months**, how many times have you seen or spoken to your **GP because of your anaemia**?

	Number of visits	Reason for visit/s
At the surgery?		
At home?		
Over the phone*? *Please only include calls made by you; not any received from your GP		

3. Thinking back **over the past three months**, how many times have you seen or spoken to a **nurse** from your local surgery **because of your anaemia?**

	Number of visits	Reason for visit/s
At the surgery?		
At home?		
Over the phone*? *Please only include calls made by you; not any received from the nurse		

Participant ID:					

4. Thinking back **over the past three months**, how many times have you used **any other health or social care because of your anaemia**?

	Number of visits	Reason for visit/s
A Home Help / Paid Care Worker?		
A Physiotherapist?		
An Occupational Therapist?		
A Speech Therapist?		
Other*?: *Please state		

APPENDIX 4: PARTICIPANT EXPERIENCE QUESTIONNAIRE

Participant ID:							Date:								
							D	D	-	M	M	-	Y	Y

Participant Experience Questionnaire – RAINDroP

1. **In your own words, could you tell us about your iron deficiency anaemia?**

2. **Tell us about your experience with oral iron tablet before you were in the study**

3. **What made you to take part in the study?**

4. **Which treatment did you receive during the study? (please circle)**
   - **A. continue oral iron**
   - **B. stop oral iron**
   - **C. stop oral iron to receive intervenous iron (iron transfusion)**

Participant ID:					

5. **What is your experience of receiving this study anaemia treatment?**

6. **How did you feel about the study anaemia treatment you received?**

7. **Was anything good or bad with the practical arrangements for your study visits? (please circle)**
   Yes / No

If yes, please state?

8. **What worked well with your study anaemia treatment?**

Participant ID:					

9. What did not work so well with your study anaemia treatment?

10. What could have helped your study anaemia treatment?

11. Please tell us if there anything else about your study experience or treating iron deficiency anaemia that you would like to add

Participant ID:					

12. read the statements below and choose one score which best describes your experience.

Tick one box each for each question

(score 1 to 5 with 1 being least/lowest and 5 being most/highest score)

Statement	1	2	3	4	5
The reason for this study is clear.					
The study is relevant to the treatment of iron deficiency anaemia.					
More research is needed for the treatment of iron deficiency anaemia.					
The written study information helped my decision to take part.					
Taking part in research is easy.					
I would recommend that other people participate in a future larger iron deficiency anaemia study.					
I would consider taking part in a study for similar issues.					

13. I am completing the survey as (Please circle)

Participant / Representative of participant

14. I have following additional comment/s to make about the study.

Please write overleaf if more space is required.