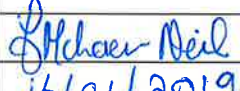
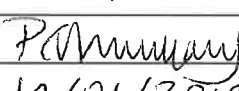


RAINDrOP: RAndomised Iron Deficiency anaemia management Pilot

Operations Manual for Trial Personnel and Recruiting Sites

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Version:	Date:	Name:	Signature:

Abbreviations

AE	Adverse Event
CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
CRF	Case Report Form
eGFR	estimated Glomerular Filtration Rate
ICF	Informed Consent Form
GCP	Good Clinical Practice
GP	General Practitioner
Hb	Haemoglobin
HIC	Health Informatics Centre (University of Dundee)
ISF	Investigator Site File
IV	Intravenous
NIHR	National Institute for Health Research
NRS	National Health Service Research Service
PCN	Primary Care Network
PI	Principal Investigator
PID	Person Identifiable Data
PIS	Participant Information Sheet
RN	Research Nurse
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TRuST	Tayside Randomisation System
UKCRN	UK Clinical Research Networks
Other	

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1. Recruiting a participant

1.1 Identifying participants

Four channels of recruitment will be employed for database (participant list) searches using the inclusion and exclusion criteria; searches will be conducted by Primary Care Network (PCN) or Research Nurse (RN):

- GP practice lists / PCN search
- Hospital clinics / RN search
- Laboratory results lists / RN
- Research volunteer databases / RN.

1.1.1 Primary Care

Primary care recruitment will be carried out with the assistance of the NRS and NIHR PCNs. In England the NIHR Ageing CRN will assist with secondary care recruitment. UKCRN portfolio recruitment accruals will be allocated according to country:

- In Scotland to NRSPCN
- In England to NIHR Ageing CRN.

1.1.2 Secondary Care

The Principal Investigator (PI) / RNs at each site should use their local knowledge to identify the appropriate clinicians, registries and networks from which to identify potential participants and target advertising. Appropriate clinicians should be provided with Clinician Invite Letter and Clinician Information. When the clinician provides agreement the localised Research Information Sheet Clinicians (RISC) will be provided; this details the Cohort Validation process that will be used prior to invitation letter mailing.

1.1.3 Advertising / Direct Contact

Targeted local advertising will also be used.

Interested individuals will contact the research team to request study information:

- Ask if an invitation letter/pack has been received
 - If yes, verbally obtain cohort ID from volunteer [found in top corner of invitation letter]; via the HIC Recruitment Tracker search for patient using cohort ID.
 - If no, RN will add the participant details to the HIC Recruitment Tracker.
 - Confirm details then follow Recruiting Participants process (Section 1.4)
 - i.e. Provide verbal/brief study information, Conduct pre-screening, If eligible and appropriate provide the Patient Information Sheet, Book Visit 1.
- OR
- Where an invitation letter is preferred and with clinician agreement (where known) the centralised invitation letter/pack process can be used (Cohort Validation Process: Prepare Identified Patient List below).

1.2 Searches and Cohort Validation Process

To identify potentially eligible participants, and with permission from the clinician / participants' doctor, the following searches will be carried out:

- Oral iron: prescribing searches will be performed by PCN / GP and RN / hospital clinician.
- Haemoglobin and ferritin results: biochemistry and haematology results listings created by the NHS laboratory will be reviewed by PCN / GP or RN / hospital clinician
- Inclusion and exclusion criteria: medical notes will be screened by the PCN / GP and RN / hospital clinician

- Prepare Identified Patient List spreadsheet, using the format below:

Clinician									
Name /									
Practice Code	NHS number	Title	First name	Surname	Date of birth	Address1	Address2	Postcode	Telephone (optional)
									Email (optional)

- Clinician screens Identified Patient List for exclusions; finalise Identified Patient List spreadsheet.
- Complete RAINdrop Cohort Validation Form; Clinician to sign.
- Transfer the following files:
Identified Patient List (excel spreadsheet) [the system requires that you password protect this file]
Validation Form
Department Headed Paper / Letterhead (word version).

Via the link <https://nww.sft.nhs.uk/sft/>

Add recipient Tay-UHB.HICrecruitment@nhs.net

- Send a separate e-mail containing the Identified Patient List password to Tay-UHB.HICrecruitment@nhs.net

1.3 Participant ID

- The Participant ID is provided by the Recruitment Tracker (cohort ID) and is only the unique study identifier.

1.4 Recruiting participants

All invitation letters will be managed and mailed by HIC. Invitation packs contain:

- Invitation letter – from GP or Clinician
- RAINdrop brochure (brief information)
- Reply slip
- Pre-paid HIC addressed return envelope.

If required, one reminder letter will be sent.

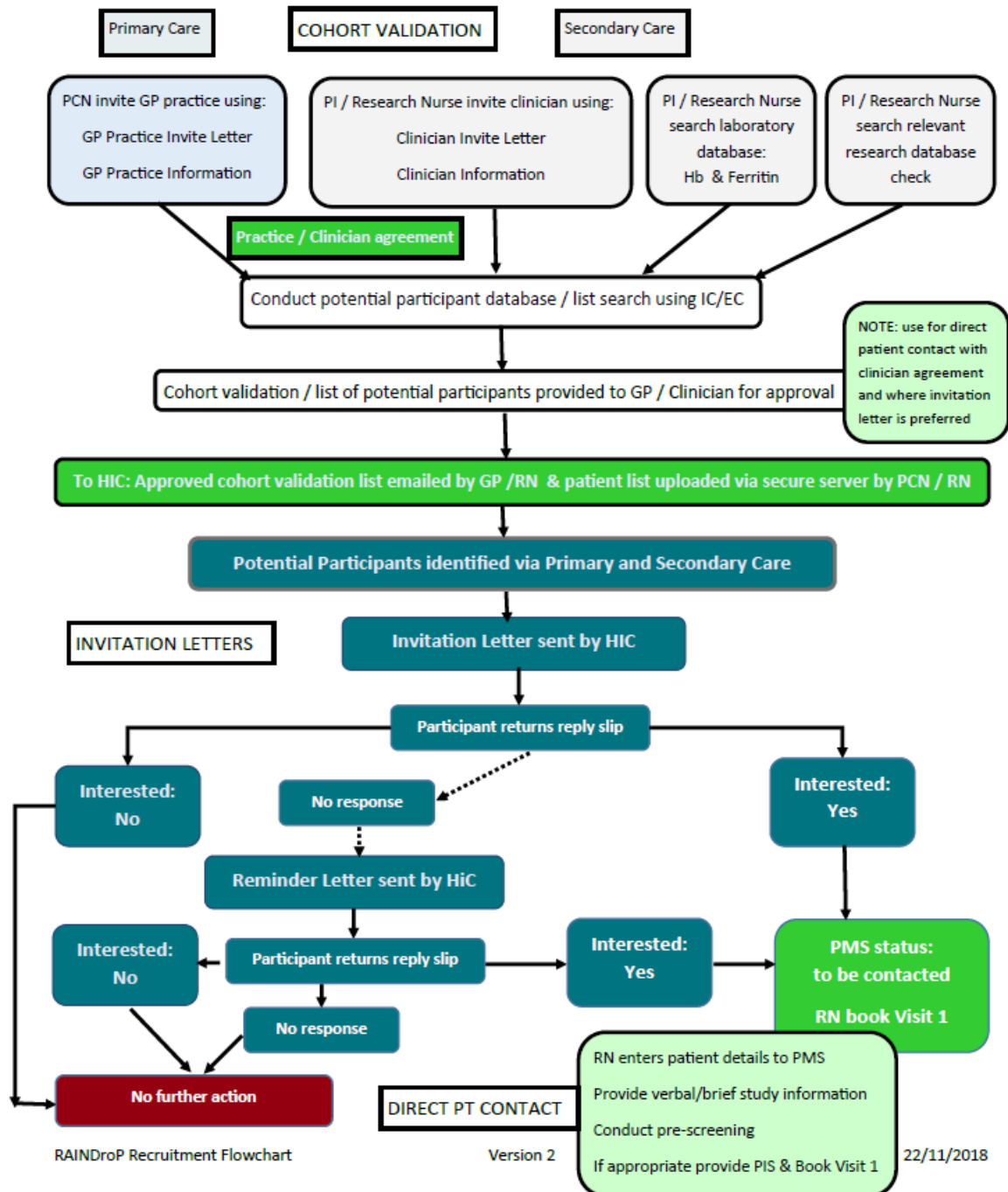
The process is summarised in the Recruitment Flowchart: Cohort Validation and Invitation Letters.

Following a request from a potential participant, for study team contact, the study team will use the Recruitment Tracker to access participant details. The research nurse will:

- telephone / email the potential participant to describe and discuss RAINdrop participation
- carry out pre-screening; check inclusion and exclusion criteria
- provide RAINdrop PIS via mail or email; potential participants should have the PIS for 24 hours before Visit 1 / informed consent.
- inform potential participants that a taxi will be provided to bring them to the appointment and return them home or if they prefer travel costs to the research visits will be reimbursed. This has been proven to help recruitment and retention of trial participants, in this age group.
- where appropriate, book Visit 1
OR
if potential participant is not eligible or declines to participate, thank them for their time and make them aware that this will not affect their future medical care.



Recruitment Flowchart: Cohort Validation & Invitation Letters



1.5 Recording Study Invites and Screening Activity

- Primary care screening activity will be reported by the PCN, to the CI.
- Secondary care participant notes screening activity will be recorded by the RN on the screening log.
- Telephone pre-screening will be recorded by the RN on the Screening Log and Recruitment Tracker.
- Visit 1 screening will be recorded by the RN on the Screening Log and Recruitment Tracker.
- Reason for ineligibility will capture the first reason / item identified and use the inclusion / exclusion list numbering (laminated sheets are be provided).
- Monthly, the Screening Log (with PID occluded) will be emailed by the RN to the RAINDroP trial coordinator.

1.6 Recruiting Participants Associated Documents

The latest versions of all documents will be found in the documents folder on the Staff Portal of the RAINDroP web site. Links to the University of Aberdeen and TASC SOPs will be found in the SOP folder on the Staff Portal / or via University of Aberdeen and TASC websites. These SOPs should not be printed out to ensure the most up-to-date versions are used.

- Invitation Letter - Clinic & GP
- RAINDroP Brochure
- Reply Slip
- Reminder Letter – Clinician & GP
- RAINDroP Participant Information Sheet
- RAINDroP Recruitment Flowchart
- Inclusion and Exclusion Criteria (laminated pages)
- Screening Log
- Clinician Invite Letter and Clinician Information
- RISP / RISC
- Potential Participant Search and HIC Transfer
- RAINDroP identified patient list (spreadsheet)
- Clinician Cohort Validation Form
- HIC Recruitment Tracker User Guide.

2. Informed Consent

2.1 Responsibility for taking informed consent

The PI has responsibility for obtaining informed consent at each recruiting centre. The PI can delegate obtaining consent to a RN, on the condition that the RN has received training in the informed consent process (GCP training) and Protocol specific training to ensure that they are sufficiently knowledgeable about the trial. This must also comply with the local Trust's Research Governance Policy. The delegation of taking consent by the RN will be entered in the Delegation of Responsibilities Log and filed in the Investigator Site File.

2.2 Taking Informed Consent

- Written consent will be taken at Visit 1 (the combined screening and baseline visit) prior to any trial related activity
- The person taking the informed consent should satisfy themselves as to the identity of participants. This should be noted in the medical notes
- Give participants an opportunity to ask any questions they may have regarding their participation in the trial
- 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
- Once satisfied that participants fully understand the nature of the trial, participants should complete the Informed Consent Form by writing their initials if they agree to each of the consent conditions.
- The Informed Consent Form should be signed and dated by the participant and the person taking the consent (PI or RN). The RN should write the Participant ID number at the top of the consent form (this can be added at the end of the visit once it is known if the participant is suitable for the study or a screen fail)
- Circulation of PIS & Informed Consent Form:
 - One copy of the PIS and Informed Consent Form should be given to the participant for their records.
 - One copy of the PIS and Informed Consent Form should be stored in the participant's medical notes.
 - The original PIS and Informed Consent Form should be filed in the Investigator Site File.
- The Informed Consent Form and Participant Information Sheet will be archived at the end of the trial for 15 years.
- A verbal consent check will be performed at each subsequent visit; recorded in participant medical record and CRF
- Complete the Enrolment and Randomisation Log in the Investigator Site File when you consent / enrol participants into the trial. Every participant consented to the trial should be included on the Enrolment and randomisation Log.
- If there are significant changes to the Participant Information Sheet during the period participants are enrolled in the trial, participants must receive a copy of the new Participant Information Sheet and re-consent. This should be filed as per circulation list above

2.3 Recording Consent

- Date of PIS provision, date and time of informed consent, and name of person taking consent will be recorded in the medical record
- Consent will be recorded by the RN on the Enrolment & Randomisation Log
- Date of consent will be recorded in the CRF
- The Participant ID is provided by the HIC Recruitment Tracker (Cohort ID)
- Monthly, the Enrolment & Randomisation Log will be emailed by the RN to the RAINDrOP trial coordinator.

2.4 Informed Consent Associated Documents

The latest versions of all documents will be found in the documents folder on the Staff Portal of the RAINDrOP web site. Links to the University of Aberdeen and TASC SOPs will be found in the SOP folder on the Staff Portal / or via University of Aberdeen and TASC websites. These SOPs should not be printed out to ensure the most up-to-date versions are used.

- Enrolment & Randomisation Log
- Informed Consent Form
- Participant Information Sheet
- Receiving informed consent SOP
- Training Record SOP
- Delegation Log.

3. Visit 1: Screening and Baseline (approx. 2 hours)

Refer to study matrix.

3.1 Participant transport

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

- When arranging patient visits, patients should be offered a taxi to bring them to the appointment and return them home. This has been proven to help recruitment and retention of trial patients in this age group.
- An account should be set up with a local taxi account for this as per local practice.
- Participants wishing to use public transport should have their cost reimbursed or petrol paid as per local practice e.g. from petty cash or by completing a travel expense form.

Site travel expense claims will be submitted to University of Aberdeen.

3.2 Informed consent

See Section 2.

3.3 Case Report Form

- Following consent the RAINDrOP CRF will be used to record participant visit data.

The CRF provides detailed completion and assessment instructions.

- Participant ID will be completed on each page of the CRF.

3.4 Concomitant medications

- Iron treatment name, dose, unit and frequency are captured at Visit 1 and Visit 4 (following assessments) on separate pages of the CRF.
 - Use the following frequency Code:
 - Once per Day = OD Twice per Day = BD Three times per day = TID
- All other prescribed medications are recorded using the generic name, at Visit 1 and Visit 4, on the Concomitant Medication page of the CRF:
 - Over-the-counter medications are not recorded
 - Ingredients of combined medications should be listed separately e.g. for Co-dydramol list codeine and paracetamol.
 - Abbreviations should not be used.

3.5 Demographic, Clinical Information and Measurements

- Ensure that participants are aged 65 or over on the date of Visit 1, to comply with inclusion criteria 3.
- Medical notes will be reviewed to assess eligibility.
- Blood results obtained from medical record / laboratory report:
 - Haemoglobin and ferritin results prior to starting oral iron; these results are required to determine eligibility:
 - Where results are not available the participant is ineligible.
 - Haemoglobin results after a minimum of 8 weeks oral iron therapy. Where not available the participant is ineligible.
 - Ferritin results reported with a decimal place will be rounded:
 - Where 0.4 and below round down e.g. 28.4 record as 28
 - Where 0.5 and above round up e.g. 28.5 record as 29

- Where ferritin result, after commencing oral iron therapy, is not available the baseline sample result is required for eligibility assessment; where not available leave pCRF result and date field blank. Refer to OpenClinica data entry notes.
- If available, and within 12 months of Visit 1, creatinine and eGFR will be used to assess eligibility; otherwise baseline sample results are required for eligibility assessment – see Section 3.6.
- Participant will be asked to describe their home circumstances (record all that apply e.g. if living alone and in sheltered housing record both) and use of care services, and where applicable number of hours per week.
- Walking aids used outside the home, record those used at Visit 1 e.g. if zimmer and stick are brought to the visit record both.
- Height and weight will be measured using local equipment and protocol; flat shoes and indoor clothing (no coats / heavy jackets) can be worn.
- BMI will be calculated using the NHS BMI calculator.
www.nhs.uk/Tools/Pages/Healthyweightcalculator.aspx
NOTE: the CRF requires measurement using meters while the calculator uses cms.

3.6 Baseline / Screening blood samples

- As per local laboratory guidance / policy samples will be collected for local laboratory haematological and biochemical analysis:
Up to 10ml of non-fasted blood for haemoglobin, ferritin, c-reactive protein, creatinine and estimated GFR (using CKI-EPI equation).
- Record taking of baseline / screening samples and results (when available) in CRF.
- Where ferritin, after commencing oral iron treatment is not available, the baseline sample result is required for eligibility assessment.
- C-reactive protein results reported with a less than symbol (<) will be recorded as the whole number below e.g. <04 record as 03.
- Creatinine and eGFR screening sample results are required to assess eligibility if results are not available within 12 months of Visit 1:
 - If these results are out with the inclusion criteria then the participant is ineligible; they should be informed and thanked for their time and made aware that this will not affect their future medical care.
The Completion of Trial / Early Withdrawal Form should be completed.
 - If results are within inclusion criteria proceed to Randomisation / Visit 2.
- Where sample/s are not obtained, this will be recorded as a deviation; use Breach and Deviation Log;
 - if ferritin, creatinine and eGRF are required for eligibility and not obtained the participant is ineligible

3.7 Medical history – other relevant medical conditions

The Medical History section should be completed as fully as possible and should be as diagnosed by a doctor.

- Relevant medical history will be recorded in the CRF, using a tick for yes or no; tick against each listed condition; tick yes where the condition has been diagnosed.
- Date of diagnosis is not required.
- Additional details are not required, i.e. do not annotate CRF to provide extra information.
- Only where other medical conditions are reported (i.e. not listed on CRF page) is a written response required. The “other medical history” should include:
 - Currently active medical conditions

- Medical conditions which the participant is receiving concomitant medications
- Past medical conditions which impact on the participants' Activities of Daily Living or ability to complete the trial assessments.
- Abbreviations should be avoided.

Medical History CRF page definitions:

TIA: Transient Ischaemic Attack

Diabetes = Type 1 or Type 2

Chronic Kidney Disease Stage 3a eGFR = 45-59mL/min (NICE CG182)

Fragility fractures: Fractures that result from low-level (or 'low energy') trauma that is caused by mechanical forces that would not ordinarily result in a fracture. The World Health Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less.

Ref: February 2012, NICE, Osteoporosis: assessing the risk of fragility fracture, NICE guideline, Draft for consultation.

BCC: Basal Cell Carcinoma

SCC: Squamous Cell Carcinoma

COPD: Chronic Obstructive Pulmonary Disease

Liver disease: yes if either (or both) cirrhosis or chronic hepatitis

Other: see above.

3.8 Inclusion/exclusion criteria

- **All participants MUST meet the inclusion and exclusion criteria prior to randomisation:**
 - If at Visit 1 any inclusion criteria is answered NO, or exclusion criteria answered YES participant is NOT eligible for the trial and must not be included in the trial. Please record Failed Eligibility on Completion of Trial Early/Withdrawal Form
 - **Exception:** where creatinine and eGFR screening blood results are awaited
 - this exclusion criteria will be completed before Visit 2 / randomisation.
- All inclusion criteria will be answered yes and all exclusion criteria will be answered no
 - Inclusion criteria 7 requires either option 'a' or 'b' to be completed.
 - Exclusion criteria: Taking oral anticoagulants (e.g. warfarin, apixoban). Antiplatelet agents are permitted (e.g. aspirin, dipyridamole, clopidogrel) – see link below for further info.
<https://bnf.nice.org.uk/treatment-summary/antiplatelet-drugs.html>
- Participants are ineligible if they are participating in another drug study, or less than 30 days since completing another drug study.
 Observational trials would not exclude a patient but the PI / RN must confirm with the other research team this would not cause any contraindications with their study.
- The final eligibility check will be performed and confirmed by the PI / medically qualified delegate at either:
 - Visit 1, the combined screening/baseline visit
 - Visit 2, prior to randomisation

This signed eligibility confirmation will be recorded in the Case Report Form (CRF) and medical notes.

3.9 Visit 1 Assessments

A series of standardised assessments are used to assess physical function and health and social activity. These should be carried out in the order provided within the CRF and trial matrix.

3.9.1 Physical Assessments

The RN administering the assessments should be familiar with the tests.

- All tests require a stopwatch and chair.
- The RN will assess safety prior to commencing each physical test
 - where a contraindication is identified do not attempt or halt the test.
- Required emergency equipment: Telephone, Oxygen Source, BP monitor / sphygmomanometer and stethoscope, (automated electronic) defibrillator.
- Prior to the Visit advise participants to:
 - wear comfortable clothing and appropriate shoes for walking.
 - Bring / use their usual walking aids during the test (stick, zimmer, etc.)
 - Continue usual medical / medication regimen.
 - Eat a light meal before early morning or early afternoon tests.
 - Avoid vigorous exercise within 2 hours of beginning the test.

Guidance for the Physical Assessments, are provided to site as laminates:

- Short Physical Performance Battery
- Six Minute Walk Test.

Short Physical Performance Battery

This validated test provided by Guralnik, Ferrucci, Salive & Wallace (1994) should take approximately 10 minutes to complete.

- Requires a clearly marked 3 metre walking course.
- Times are recorded as seconds, to one decimal place.

The test will be completed in the order and as described in the CRF.

- Prior to undertaking each assessment the RN will demonstrate and clearly describe the activity using the bold italic text; the participant will be given the opportunity to ask questions and confirm agreement.
- Where a test is not completed:
 - provide number of seconds and reason for failure/not attempted
 - proceed to next test e.g. if gait speed not completed go to chair stand (as instructed in CRF).

The RN is not required to complete scoring.

A SPPB instructional video (provided by Division of Geriatrics, University of California San Francisco) and additional SPPB tips video (National Institute on Aging, Dr J Guralnik) are recommended; training should be recorded on the Study Specific Training Log.

Six-minute walk test

- Requires:

30 metre flat walking area with 3 metre interval markings and brightly coloured tape or cones to mark boundaries of course.

- Where turnaround points are required these will be clearly identified and recorded each time the turnaround or starting line is crossed.

Temporary marker to mark and measuring tape to measure finish point.

Chairs at regular (30 metre) intervals are advised. [Note: Rests / stops are not permitted; this will end the test].

- The test will be completed as described in the CRF

- Prior to undertaking the assessment the RN will clearly describe the activity using the bold italic text and demonstrate one lap; the participant will be given the opportunity to ask questions and confirm agreement.
- Start the stopwatch when the participant moves their foot to take their first step.
- The RN should walk behind the participant to so that they do not affect their pace.
- Provide standardised encouragement at 1, 3 and 5 minutes:
 - 1 min - You are doing a good job
 - 3 min - You've reached halfway
 - 5 min -You have one minute to go.
- Where participant stops and less than 6 minutes are walked record distance achieved and time as minutes and seconds, i.e. if 4 minutes 23 record 4.23.

The 6 minute walk test is described the American Thoracic Society (2002) and summarised by Bittner V & Singh S (The Cardiology Advisor).

3.9.2 Questionnaire Research Tools

Guidance notes for the completion of the Questionnaire Tools are provided on each tool.

- The following questionnaires and scoring tools should be completed by the participant and returned to the RN at the end of Visit 1
 - Oral Iron Use Scale
 - Fatigue Severity Scale
 - Participant Reported Anaemia Symptoms
 Additionally forms are given to the participant to complete at the end of Month 1 and Month 2
- At end of Visit 1, RN to provide Participant Reported Anaemia Symptoms Questionnaire for Month 1 and Month 2.
 - EQ-5D (Quality of Life)
 - 15D (Health Related Quality of Life)
 - Activities of Daily Living (Nottingham EADL score)
 - Health & Care Use questionnaire.
- Indicate completion in the CRF.
- Where the visual analogue score response provides a range of values, the value in the middle should be recorded on OpenClinica.
 - NOTE: EQ5D requires a numerical value to be provided in addition to the cross on the visual analogue scale. Prior to the end of the visit the RN should check that the value provided matches the scale; where the value does not match or has not been provided the RN can request that the participant updates/completes the value field. Where the value field has not be completed the middle value will be recorded on OpenClinica.

3.10 Prior to the end of the Visit 1: Information for the Participant

- Schedule Visit 2
- Advise possible dates for Visit 3
- Schedule Visit 4
- Provide Study Participant / Appointment Card (provides team contact details)
- Participant Reported Anaemia Symptoms Questionnaires for completion at end of Month 1 and Month 2
- Provide copy of PIS and signed Informed Consent Form.

3.11 Significant Clinical Finding

- If a significant clinical finding is identified the PI / medically qualified delegate will be informed and they should take the appropriate action according to their clinical opinion.
- A letter with details of the finding and any actions taken will be completed and sent to the patient's GP and a copy filed in the medical notes.

3.12 Failed Screening

- If the participant is deemed ineligible "Early Withdrawal Form" should be completed.
- The reason for failed screening should be recorded on the CRF and RAINDrop Screening Log.

3.13 Recording Visit 1

- The Screening & Baseline Visit will be documented in the patients' medical notes [checklists are provided] and should include the following information for source data verification:
 - Copy of signed Informed Consent Form.
 - Copy of Patient Information Sheet provided.
 - Date of visit.
 - Confirmation that the patient has had the PIS for at least 24 hours.
 - Confirmation of how patient identity was verified.
 - Details of any notable findings at the visit and any action taken.
 - Confirmation that all inclusion/exclusion criteria were met; and if results are awaited.
 - Height and weight.
 - File a copy of blood results, signed by PI.
 - Confirmation that the visit was carried out as per protocol.
 - Name and Signature of Research Nurse completing the visit.

3.14 Data Entry

- Data collected by the RN/delegated and/or the PI will be recorded on the paper CRF.
- Data from the paper CRF will be entered on the RAINDrop electronic database, OpenClinica.
- Oral Iron Use Scale responses are entered on the Oral Iron Use Excel spreadsheet (to maintain blinding).
- Data entry should be completed within 10 days working days of the visit.
- Visit scheduling data is recorded on the Recruitment Tracker.
- Screen fail data is not transferred to OpenClinica.
- OpenClinica data entry notes provide detailed guidance.

3.15 Visit 1 Screening & Baseline associated documents

The latest versions of all documents will be found in the documents folder on the Staff Portal of the RAINDrop web site. Links to the University of Aberdeen and TASC SOPs will be found in the SOP folder on the Staff Portal / or via University of Aberdeen and TASC websites. These SOPs should not be printed out to ensure the most up-to-date versions are used.

- Enrolment & Randomisation Log
- Training Record SOP
- Delegation Log
- RAINDrop Training Log & SOP Sign-off Sheet
- Screening Visit Checklist (for medical notes)
- Preparing and maintaining CRFs SOPs
- Data management using Excel SOP

- HIC Recruitment Tracker User Guide
- OpenClinica user guide.

4. Follow-up visits

Refer to study matrix

4.1 Adverse events (AE)

See Protocol Section 10

- AEs will be collected at Visit 2 and Visit 4.

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 at each and every study visit.
- 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.

- AEs will be assessed by the PI / medically qualified delegate for:
 - severity, causality and seriousness.

4.1.1 Assessment of Causality

The Principal Investigator must make an assessment of whether the AE/SAE is likely to be related to the intervention according to the following definitions:

- Unrelated: where an event is not considered to be related to the intervention.
- Possibly: although a relationship to the intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the intervention.
- Definitely: The known effects of the intervention, or based on challenge testing, suggest that the intervention is the most likely cause.

Reference safety information, Summary of Product Characteristics, for each of the oral and IV iron preparations are provided via the RAINDrOP website.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the intervention will be considered as ARs/SARs.

All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the intervention and another drug will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

4.1.2 Assessment of Severity

The Principal Investigator should make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

- Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

- Severe: an event that prevents normal everyday activities.

The term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

4.1.3 Assessment of Expectedness & Suspected SAE

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

- The PI will sign and date each AE entry on the CRF AE log.
- Where a suspected / SAE occurs and within 24 hours of an investigator becoming aware of the event, the RAINDrop SAE form will be completed by PI or delegate then emailed to phyo.myint@abdn.ac.uk, cc raindroptm@dundee.ac.uk

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), 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 Protocol Reference Safety Information (Protocol Section 6.3) as an expected occurrence.

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.

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.

4.2 Concomitant medications

- Follow-up concomitant medications are collected at Visit 4.
To maintain blinding iron treatment / oral iron use data is collected after Visit 4 assessments are completed.

4.3 Visit 2: Randomisation (1 - 4 days after Visit 1)

When the PI / medically qualified delegate has completed the final eligibility assessment and the confirmatory CRF Participant Eligibility sign off the RN can proceed to randomisation.

- Site codes

Professor Phyo Myint	Aberdeen	ARI
Dr Vera Cvorovic	Fife	FIF
Dr Miles Witham	Newcastle	NWC
Dr Helen May	Norfolk & Norwich	NUH

- The **UNBLINDED** Research Nurse will access the web-based randomisation system TRuST.
The following information is required for randomisation:
 - Haemoglobin result after 8 weeks of oral iron

- Ferritin prior to starting oral iron (rounded as per section 3.5)
- 6 minute walk test distance
- Randomisation will allocate one of three possible interventions:
 - Treatment as usual
 - Stop oral iron treatment
 - Stop oral iron and give IV iron (as per local formulary).

4.1.3 Emergency Randomisation

- Where web-access is not possible at site, emergency randomisation will be provided by TCTU, via telephone 01382 383581.
A high importance email should also be sent to raindroptmdundee.ac.uk
- TCTU will require the following participant data to complete randomisation:

Participant ID:	(6 digit Cohort ID)		
Randomisation Variable(s) (from IWRS specification doc)	Haemoglobin g/L	Ferritin ug /L	6 minute walk distance m
Variable outcome: (provided by person requesting randomisation)	Actual value	Actual value	Actual value
Participant Meets Eligibility Criteria:	<ul style="list-style-type: none"> • Currently taking oral iron at any does with a minimum of 8 weeks therapy? <i>(must be yes)</i> • Insufficient response to oral therapy? <i>(must be yes)</i> • PI signed to confirm eligibility? <i>(must be yes)</i> 		
Randomised By:			
Randomised Date:			

- Treatment allocation will be notified during the telephone call and by email; a copy of the email will be printed (as per 5.3.2).

4.4 Visit 2: Telephone call (1 - 4 days after Visit 1)

UNBLINDED Research Nurse activity.

- Telephone participant.
- Confirm continued participant consent.
 - If participant wishes to continue, follow the process detailed in the Intervention Instructions Table (below) according to which group the participant has been allocated to. (arrange visit 3 for IV iron where required)
 - If withdrawal, complete Study Withdrawal page, indicate reason for Early Withdrawal.
- Record any adverse events.

Intervention Instructions Table

Treatment Arm	Instruction
Group 1: Continue oral iron	1. Telephone participant and instruct to continue oral iron
	2. Send recruited letter to GP informing Group 1 allocation Oral iron continuing for study duration
Group 2: Stop oral iron	1. Telephone participant and instruct to stop oral iron
	2. Send recruited letter to GP informing Group 2 allocation Oral iron stopping for study duration
Group 3:	1. Arrange appointment with Day Hospital / Clinical facility

Stop oral iron & give IV iron	<i>Following discussion with participant this may need to be re-arranged</i>
	2. Telephone participant, instruct to stop oral iron. 3. Advise and confirm appointment to attend for IV infusion <i>IV infusion visit should be within 2 weeks of randomisation</i>
	4. Send recruited letter to GP informing Group 3 allocation Oral iron stopping & IV iron therapy for study duration and not to restart oral iron for 3 months

4.5 Informing a GP about study entry and treatment allocation

The GP Letter - Recruited will be sent following Visit 2 telephone call.

- RN will complete the following details:
 - Date
 - GP name
 - Participant details (name, date of birth and 6-digit unique participant study identifier)
 - Date of randomisation
 - Treatment allocation group 1, 2, or 3
 - For participants allocated to group 3, location for IV iron visit
 - Research Nurse contact information
- A copy of the GP Letter – Recruited will be filed in the medical record.

4.6 Visit 3: IV iron infusion (within 2 weeks of Visit 2)

- Arrange taxi or advise participant that transport costs shall be reimbursed (See Section 3.1).
- The PI / or medically qualified delegate will prescribe the IV iron as per local policy; dose and time are calculated using weight and Hb level.
- The infusion will be administered by a Registered Nurse / appropriately qualified member of the NHS team in an appropriate clinical location with NHS emergency facilities.
- The local NHS IV iron policies and procedures will apply during and after the procedure, this can include:
 - medical notes record of the procedure (to avoid unblinding, where possible the blinded RN should avoid reviewing the medical record until after Visit 4 assessments are completed).
 - the patient receiving NHS IV iron infusion information prior to discharge
 - repeat haemoglobin and ferritin levels
 - where response is sub-optimal a repeat infusion may be required.
- The **UNBLINDED** RN will attend the IV iron infusion visit to:
 - Confirm participant consent
 - Record any adverse events.
- IV iron treatment data will be recorded in the Iron Treatment log and excel spreadsheet after Visit 4 assessments have been completed.

4.7 Visit 4: 3 Month Follow Up (+/- 3 weeks)

BLINDED RN activity.

- Arrange taxi or advise participant that transport costs shall be reimbursed (See Section 3.1).

- Confirm continued participant consent.
- **Do not ask about any adverse events/medications until after the assessments have been completed.**

4.7.1 Follow up Blood Samples

- As per local laboratory guidance / policy samples will be collected for local laboratory haematological and biochemical analysis:
Up to 5ml of non-fasted blood for haemoglobin and ferritin.
- Record taking of follow up samples and results (when available) in CRF.
- Where sample/s are not obtained, leave pCRF results field blank; this will be recorded as a deviation; use Breach and Deviation Log.
- Where Ferritin result is reported with a decimal point, rounding as per section 3.5.

4.7.2 Physical Assessments

The RN administering the assessments should be familiar with the tests.

- All tests require a stopwatch and chair.
- The RN will assess safety prior to commencing each physical test
 - where a contraindication is identified do not attempt or halt the test.
- Required emergency equipment: Telephone, Oxygen Source, BP monitor / sphygmomanometer and stethoscope, (automated electronic) defibrillator.
- Prior to the Visit advise participants to:
 - wear comfortable clothing and appropriate shoes for walking.
 - Bring / use their usual walking aids during the test (stick, zimmer, etc.)
 - Continue usual medical / medication regimen.
 - Eat a light meal before early morning or early afternoon tests.
 - Avoid vigorous exercise within 2 hours of beginning the test.

Guidance for the Physical Assessments, are provided to site as laminates:

- Short Physical Performance Battery
- Six Minute Walk Test.

Short Physical Performance Battery

This validated test provided by Guralnik, Ferrucci, Salive & Wallace (1994) should take approximately 10 minutes to complete.

- Requires a clearly marked 3 metre walking course
- Times are recorded as seconds, to one decimal place.

The test will be completed in the order and as described in the CRF

- Prior to undertaking each assessment the RN will demonstrate and clearly describe the activity using the bold italic text; the participant will be given the opportunity to ask questions and confirm agreement.
- Where a test is not completed:
 - provide number of seconds and reason for failure/not attempted
 - proceed to next test e.g. if gait speed not completed go to chair stand (as instructed in CRF).

The RN is not required to complete scoring.

A SPPB instructional video (provided by Division of Geriatrics, University of California San Francisco) and additional SPPB tips video (National Institute on Aging, Dr J Guralnik) are recommended; training should be recorded on the Study Specific Training Log.

Six-minute walk test

The 6 minute walk test is described the American Thoracic Society (2002) and summarised by Bittner V & Singh S (The Cardiology Advisor).

➤ Requires:

30 metre flat walking area with 3 metre interval markings and brightly coloured tape or cones to mark boundaries of course.

- Where turnaround points are required these will be clearly identified and recorded each time the turnaround or starting line is crossed.

Temporary marker to mark and measuring tape to measure finish point.

Chairs at regular (30 metre) intervals are advised. [Note: Rests / stops are not permitted; this will end the test].

- The test will be completed as described in the CRF
- Prior to undertaking the assessment the RN will clearly describe the activity using the bold italic text and demonstrate one lap; the participant will be given the opportunity to ask questions and confirm agreement.
- Start the stopwatch when the participant moves their foot to take their first step.
- The RN should walk behind the participant to so that they do not affect their pace.
- Provide standardised encouragement at 1, 3 and 5 minutes:
 - 1 min - You are doing a good job
 - 3 min - You've reached halfway
 - 5 min -You have one minute to go.
- Where participant stops and less than 6 minutes are walked record distance achieved and time as minutes and seconds, i.e. if 4 minutes 23 record 4.23.

4.7.3 Questionnaire Research Tools

Guidance notes for the completion of the Questionnaire Tools are provided on each tool.

The following questionnaires and scoring tools should be completed by the participant and returned to the RN at the end of Visit 4, Follow Up:

- Fatigue Severity Scale
 - Participant Reported Anaemia Symptoms
- Collect end of Month 1 and Month 2 Participant Reported Anaemia Symptoms
- EQ-5D (Quality of Life)
 - 15D (Health Related Quality of Life)
 - Activities of Daily Living (Nottingham EADL score)
 - Health & Care Use questionnaire
 - Participant experience and views.
- For participants randomised to receive oral iron the UNBLINDED RN will telephone the participant to complete the Oral Iron Use Scale.
 - Indicate completion in the CRF
 - Where the visual analogue score response provides a range of values, the value in the middle should be recorded on OpenClinica.
 - NOTE: EQ5D requires a numerical value to be provided in addition to the cross on the visual analogue scale. Prior to the end of the visit the RN should check that the

value provided matches the scale; where the value does not match or has not been provided the RN can request that the participant updates/completes the value field. Where the value field has not be completed the middle value will be recorded on OpenClinica.

4.7.4 Adverse Events

See section 4.1

- Following completion of Visit 4 assessments Adverse Events will be collected and recorded in the CRF.

4.7.5 Concomitant medications

See section 4.2

- Following completion of Visit 4 assessments iron treatment taken between Visit 1 and Visit 4 are collected. Generic name, dose, unit and frequency are collected and recorded on the separate iron treatment excel spreadsheet.
 - Use the following frequency Code:
 - Once per Day = OD Twice per Day = BD Three times per day = TID.
- All other prescribed medications that are taken at the time of Visit 4 are recorded using the generic name, on the Concomitant Medication page of the CRF:
 - Concomitant Medication taken after Visit 1 and before Visit 4 are not recorded, e.g. antibiotics.
 - Over-the-counter medications are not recorded
 - Ingredients of combined medications should be listed separately e.g. for Co-dydramol list codeine and paracetamol.
 - Abbreviations should not be used.

4.7.6 Prior to the end of Visit 4: Information for the Participant

- Provide Iron Specific Dietary Advice Leaflet
- Advise participant to contact GP; GP resumes care and iron prescribing.

4.8 Significant Clinical Finding

- If a significant clinical finding is identified at any research visit the PI / medically qualified delegate will be informed and they should take the appropriate action according to their clinical opinion.
- A letter with details of the finding and any actions taken will be completed and sent to the patient's GP and a copy filed in the medical notes.

4.9 Withdrawals

See protocol section 5.5.2

Any physician using their clinical judgement may withdraw a participant from their randomised treatment. This may occur due to occurrence of:

- Adverse Event (log on AE log)
- Onset of a symptom deemed related to study participation or procedures
- Onset of an exclusion criteria
- Any other reason which in their clinical judgement requires withdrawal.

With consent participants will continue with safety follow up and outcome measure assessments.

4.9.1 Recording Withdrawals

Document withdrawals using the CRF Early Completion / Withdrawal page and medical notes.

4.10 Recording Visits 2, 3 and 4

- Visit 2 (Randomisation and Telephone Call) will be documented in the medical notes [checklists are provided] and should include the following information for source data verification:
 - Date and time of visit
 - Verbal confirmation of consent
 - Treatment allocation
 - GP letter – Recruited
 - Name and Signature of RN completing the visit.
- Visit 3 will be documented in the medical notes and should include the following information for source data verification:
 - Date and time of visit
 - IV Iron prescription will be filed according to local policy
 - Verbal confirmation of consent
 - Details of any notable findings at the visit and any action taken.
 - Name and Signature of RN completing the visit.
- Visit 4 will be documented in the medical notes and should include the following information for source data verification:
 - Date and time of visit
 - Verbal confirmation of consent
 - Details of any notable findings at the visit and any action taken.
 - Confirmation that the visit was carried out as per protocol.
 - File a copy of blood results, signed by PI.
 - Name and Signature of RN completing the visit.

4.11 Data Entry

- Data collected by the RN/delegated and/or the PI will be recorded on the paper CRF.
- Data from the paper CRF will be entered on the RAINDroP electronic database, OpenClinica.
- Quarantined Data: the following data will be held at site until post-database lock TCTU will request site to upload via LabKey:
 - Oral Iron Use Scale responses are entered on the Oral Iron Use Excel spreadsheet (to maintain blinding).
 - Iron Treatment Data will be entered on the Iron Treatment Data excel spreadsheet.
 - Patient Experience Questionnaires will be uploaded as a zip file
- Data entry should be completed within 10 working days of the visit.
- Visit scheduling data is recorded on the Recruitment Tracker.

Refer to Excel Spreadsheet SOP for file naming, saving and back-ups.

4.12 Follow-up Visits associated documents

The latest versions of all documents will be found in the documents folder on the Staff Portal of the RAINDroP web site. Links to the University of Aberdeen and TASC SOPs will be found in the SOP folder on the Staff Portal / or via University of Aberdeen and TASC websites. These SOPs should not be printed out to ensure the most up-to-date versions are used.

- Delegation Log
- GP Letter – Recruited
- Iron Specific Dietary Advice Leaflet
- Visit Checklists (for medical notes)

- Adverse Events SOP
- RAINdrop HRA safety report form non-CTIMP
- Preparing and maintaining CRFs SOP
- Training Record SOP
- RAINdrop Training Log & SOP Sign-off Sheet
- OpenClinica user guide
- Data management using Excel SOP
- HIC Recruitment Tracker User Guide.

5. RAINdrop Systems

5.1 Website:

www.raindrop.org.uk

The RAINdrop website has two functions:

- a public section to inform potential patients, of iron deficiency anaemia; introducing the trial, the trial team and how they can get involved
- a staff section which allows access to the informatics and data management systems for the trial.

To access the staff area of the website click on Staff Portal tab.

This then gives access via a user name and password.

5.1.1 Staff Portal

The Staff Portal is the secure webpage where trial staff can access:

- HIC Recruitment Tracker – live and test site
- TRuST – live and test site
- OpenClinica data management system – live and test site
- Trial documents both generic and site specific: The trial documents section will only hold the latest version of documents and it is recommended that this is used to ensure staff are working to the latest versions.
- Accrual numbers will be available here
- Trial announcements
- Calendar for any trial events.

5.2 Recruitment Tracker

- Access the live site via the RAINdrop website or via the following link

<https://hicservices.dundee.ac.uk/Recruitment/>

The tracker is a web-based software application developed by HIC for tracking patient recruitment:

- From the initial stages of cohort identification.
- Through enlistment of GP Practices.
- Sending patient invitation letters and into study participation.

The research team do not see any participant names/ addresses until a positive response is received at HIC and updated on the tracker, which releases the contact details to the research team.

This automated, web-based system will ensure it is quick and easy for study team members to track progress of their study recruitment, potentially through multiple recruitment channels (e.g. GP practices, clinics), whilst keeping patient data secure).

A password protected user account will be activated following Site Initiation training and the completion of dummy data entry.

Where site staff use the tracker for additional studies they will see each study when they are at the home page.

5.2.1 Test Site

The RAINdrop Test Site is provided for training purposes. Access via RAINdrop website Recruitment Tracker Test site (see below)

Dummy data will be entered prior to active site access being granted.



Recruitment Tracker



[Home](#)
[Change Password](#)
[Logout](#)

Project Name	To Be Contacted	Completed Study	Declined	Withdrawn	
adAPT Glasgow	0	0	0	0	Open
adAPT Grampian	0	0	0	0	Open
Adapt Index Patients	305	0	0	0	Open
adAPT Inverness	0	0	0	0	Open
adAPT Lanarkshire	0	0	0	0	Open
adAPT North East	0	0	0	0	Open
adAPT TEST Project	8	0	0	0	Open
adAPT West Ayr	0	0	0	0	Open
ECLS Glasgow	3	321	966	70	Open
ECLS Lanarkshire	0	52	114	6	Open
ECLS Tayside	0	121	171	20	Open
PACT	0	0	36	14	Open
RAINDrop Test Site	1	0	0	0	Open

[Download User Guide](#)


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5.2.2 RAINDrop Site


Project Summary

At the home page select RAINDrop to navigate to the Project Summary.

Each site can view their summary of participants to be contacted, Visit 1 booked, consented, randomised, Visit 2 booked, Visit 4 booked and Early withdrawals.



Recruitment Tracker



[Home](#)
[Summary](#)
[Patient Search](#)
[Manage Availability](#)
[Appointment Sheet](#)
[Information](#)
[Reports](#)
[Change Password](#)
[Logout](#)

Current project: RAINDrop Test Site

Project Summary

Identified for Study

Status	Total	Self-referral 1
Positive	3	3
Overall	3	3

Awaiting GP Response
No summaries found.

Letter Sent
No summaries found.

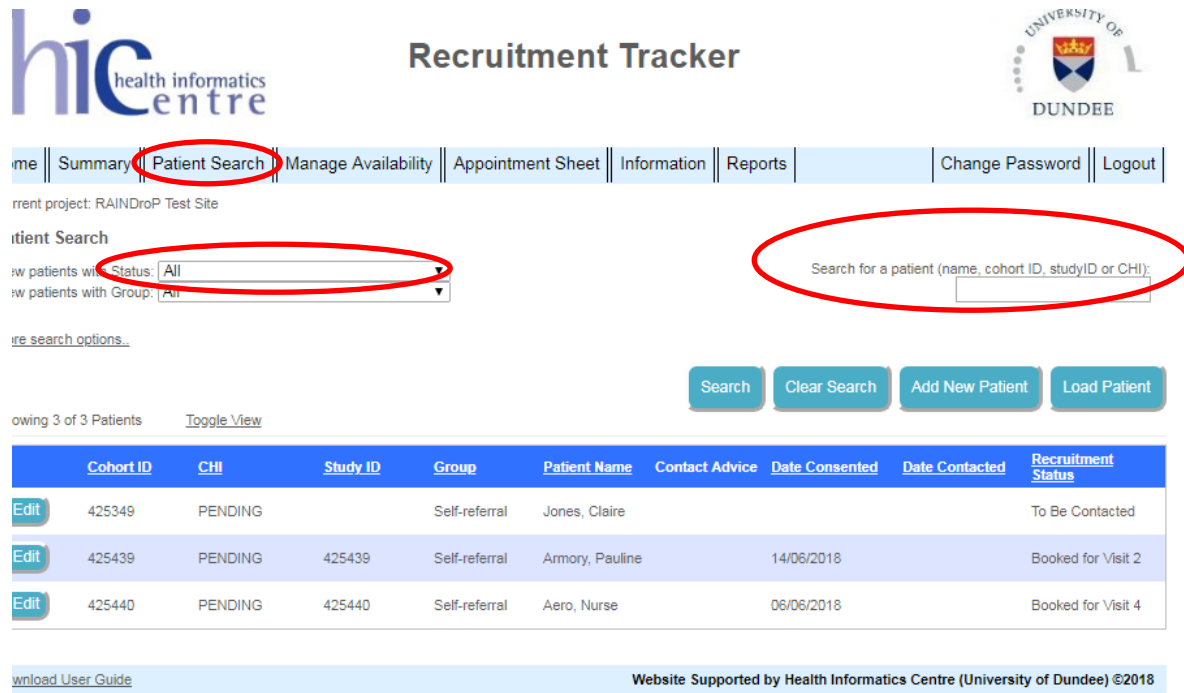
Agreed to Be Contacted

Status	Self-referral 1
To Be Contacted	1
Secondary Contact	
To be booked	
Consented	
Randomised	
Booked for Visit 1	
Booked for Visit 2	1
Booked for Visit 4	1
Early Withdrawal	

Patient Search

Selecting patient search allows users to search by patient name, cohort ID or CHI.

- Filter by Status e.g. to be contacted, ineligible, withdrawn, to book Visit 4 will further



Recruitment Tracker

Summary **Patient Search** Manage Availability Appointment Sheet Information Reports Change Password Logout

Current project: RAINdrop Test Site

Patient Search

How patients will be contacted: Status: All

How patients will be grouped: All

Search for a patient (name, cohort ID, studyID or CHI):

Search Clear Search Add New Patient Load Patient

Showing 3 of 3 Patients [Toggle View](#)

	Cohort ID	CHI	Study ID	Group	Patient Name	Contact Advice	Date Consented	Date Contacted	Recruitment Status
Edit	425349	PENDING		Self-referral	Jones, Claire				To Be Contacted
Edit	425439	PENDING	425439	Self-referral	Armory, Pauline		14/06/2018		Booked for Visit 2
Edit	425440	PENDING	425440	Self-referral	Aero, Nurse		06/06/2018		Booked for Visit 4

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Patient Details

Further to a Patient Search the Patient Details field will be displayed.

Scottish Sites:

Where a patient contacts the research team CHI will show PENDING until this data has been checked and provided by HIC (usually within a few hours).

English Sites:

CHI is not used, this will remain PENDING

Current project: RAINDrop Test Site

Patient Details Patient Appointments Patient Audit

Update and Return to Search Update

Cohort ID:	425439		
Study ID:	425439	Group:	Self-referral
CHI:	PENDING	Recruitment Status:	Booked for Visit 2
Forenames:	Pauline	Surname:	Armory
Address:	Anytown	Postcode:	DD2 1UB
Phone No. 1:	0123456789	Phone No. 2:	0123456789
Date of Birth:	01/02/1940 (Age: 78)	Email:	hello@abc.com
Contact Advice:			
GP:	SIMD:		
GP Practice:	Letter Printed Date:		
Date Updated:	19/06/2018	Date Contacted:	
Location:		Source:	Primary Care
Date PIS Given:	12/06/2018	Date Consent Given:	14/06/2018

5.3 TRuST

➤ Unblinded RNs will access via the RAINDrop website / Staff Portal or following link
<https://hicservices.dundee.ac.uk/TRuST/>

An Emergency Randomisation facility is provided by TCTU (see section 4.3).

5.3.1 TRuST Test Site

The RAINDrop Test Site is provided for training purposes. Access via RAINDrop website Training tab. Dummy data will be entered prior to active site access being granted.

5.3.2 TRuST Site

➤ enter username and password



LOG IN

Please enter your username and password.

Your login attempt was not successful. Please try again.

Account Information

Username:
tRainDrop

Password:
●●●●●●

Log In

Reset password



CHANGE PASSWORD

Use the form below to change your password.

New passwords are required to be a minimum of 6 characters in length.

Account Information

Old Password:

New Password:

Confirm New Password:

Randomise Participant

RANDOMISATION

Enter Eligibility Criteria

RANDOMISE PARTICIPANT

Eligibility Criteria

Currently taking oral iron at any dose with a minimum of 8 weeks therapy? ☐ Yes ☐ No

Insufficient response to oral iron therapy? ☐ Yes ☐ No

Venous blood Hb level?

Venous blood ferritin level?

6 minute walk distance?

Enter Participant ID (from Recruitment Tracker / Cohort ID), confirm eligibility questions then Randomise

RANDOMISE PARTICIPANT

Site: Test Site

Participant ID:

Hb g/L: ☒ ≥ 100 g/L

☐ < 100 g/L

Ferritin ug/L: ☒ ≥ 50 ug/L

☐ < 50 ug/L

6 minute walk distance: ☒ ≥ 300 m

☐ < 300 m

Has the CI/PI signed CRF to confirm eligibility of participant? ☒ Yes ☐ No

Does the participant meet eligibility criteria? ☒ Yes ☐ No

Randomise

[Return to Main Menu](#)

Intervention Allocation

RANDOMISE PARTICIPANT

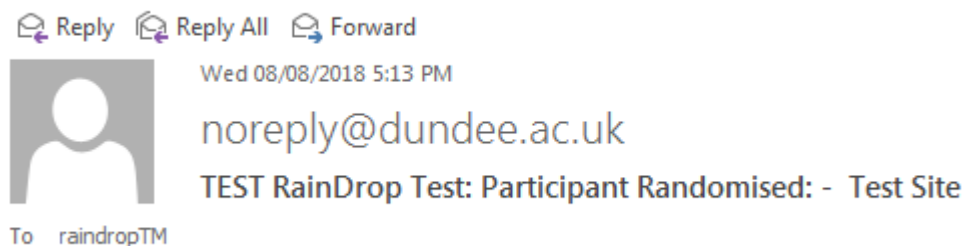
Site: Test Site

Subject Identifier: 123456

Randomisation Allocation: continue oral iron

[Return to Main Menu](#)

Print and file in medical notes the Intervention Allocation Email



Participant: 123456

Site: Test Site

Treatment: continue oral iron

Randomised By: tRainDrop

5.4 OpenClinica

OpenClinica is the data entry system for the RAINDrop trial. The RN will be responsible and ensure that all CRF data is entered via this site. Data should be entered into OpenClinica within 10 working days of the patient's visit.

OpenClinica training, provided by TCTU, will be delivered to at least one RN from each site. Dummy data will be provided to demonstrate competence. Certificate of Training will be provided for the user to file in their Training Record. A record of this training should be entered into the Study Specific Training Log.

Cascade training for other members of staff can be carried out by the RN, with agreement from the TM.

When the person entering the data into OpenClinica ticks the box to say that the CRF is complete this signifies that they are confirming that the data entered is correct and complete; subsequent data changes will require TCTU input.

See OpenClinica Users Guide and data entry notes for detailed use of the system.

- Access OpenClinica via RAINDrop website / Staff Portal.

5.5 LabKey

LabKey is a Web-based Data Repository.

TCTU will provide training prior to provision of

- Password protected user accounts.

Refer to the RAINDrop LabKey User Guide for full instructions, including folder structure and document naming convention.

LabKey will be used for:

- Quarantined data:
 - Excel Spreadsheets: Oral Iron Use & Iron Treatment Data
 - Participant Experience Questionnaire
 - Completed CRFs
 - Data Query Resolutions.
- Access LabKey via RAINdroP website / Staff Portal.

5.6 Monthly Logs and Essential Activities

- RN will receive monthly request to email the following RAINdroP Logs to the RAINdroP Trial Coordinator:

Screening
Enrolment & Randomisation
Deviations
Delegation (if any team changes)

- RN is responsible for providing data via OpenClinica, Recruitment Tracker and LabKey:

Completed CRF pages upload via LabKey
Data Verification spreadsheet upload via LabKey
Data queries / cleaning

Quarantined Data Uploads:

Oral iron Use and Iron Treatment Data Excel Spreadsheets
Participant Experience Questionnaire

Data entry is required within 2 weeks of a study visit. Where this is exceeded a deviation should be recorded on the Deviation Log.

- The RN, or delegate, is responsible for Investigator Site File maintenance. Printed documents, including correspondence with TM and RAINdroP Trial Coordinator will be filed according to the ISF index.

5.7 Associated Documents

- The latest versions of all documents can be found in the generic documents folder on the Staff Portal. Links to the TASC SOPs can be found in the SOP folder on the Staff Portal. These SOPs should not be printed out to ensure the most up-to-date versions are used.
 - OpenClinica user guide
 - Data management using Excel SOP
 - HIC Recruitment Tracker User Guide.

6. Deviations and Breaches

6.1 Definitions

- A Breach is a departure from the approved protocol, research project documentation, SOPs or any other information relating to the conduct of the trial.
 - A Non-Serious Breach may be considered a 'minor non-conformance' or 'violation' and has no impact on a participant's safety or wellbeing, and/or the scientific integrity of the research. No substantial amendment is required to the approved protocol, trial documentation or trial SOPs. Examples of A Non-Serious Breach include:
 - A study visit out with a defined schedule.
 - Boxes on the consent form ticked rather than initialled.
 - Misplaced consent form (completed but mis-filed).

A Non-Serious Breach may be upgraded, upon review, to a Serious Breach. It should be noted that repeated Non-Serious Breaches which become systematic, or impact multiple participants, may be regarded as a Serious Breach and should be reported as such.

- A Serious Breach is defined as a Breach which is likely to affect, or have the potential to affect, to a significant degree:
 - The safety, physical or mental integrity of the research participants and/or
 - The scientific value of the research.
 - Examples of a Serious Breach include:
 - Persistent non-compliance with GCP or protocol.
 - Fraud relating to clinical trial records or data.
 - Breach leading to the death, hospitalisation or permanent disability of a participant.
 - Failure to report serious adverse events.
 - Lack of essential approvals.
- A Deviation is a minor deviation from an SOP or a planned event. Examples include:
 - Failure to collect a self-report questionnaire
 - A rescheduled trial visit.
 - Participant refusal to complete scheduled research activities.
 - An SOP being used beyond its review date.
 - An audit or monitoring visit taking place outside of schedule.

A Deviation may be upgraded, upon review, to a Non-Serious Breach or Breach.

- An Urgent Safety Measure occurs when a research participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant(s). An Urgent Safety Measure does not have prior approval from REC or the Sponsor. Urgent Safety Measures must be reported to REC and Sponsor immediately after they are implemented.

Deviations, Breaches and Urgent Safety Measures shall be recorded in such a way that their impact on the research project can be independently assessed during the conduct,

reconstruction and reporting of the trial. Full details shall include any corrections and Corrective and Preventive Actions (CAPA) identified.

- Relationship between a Deviation, Non-Serious Breach and Serious Breach. Deviation Non-Serious Breach Serious Breach



- A Deviation shall be reviewed by the Research Governance Team and/or Quality Assurance and may be upgraded to a Non-Serious Breach.
- A Non-Serious Breach shall be reviewed by Research Governance Team and/or Quality Assurance and may be upgraded to a Serious Breach, or downgraded to a Deviation.
- A Serious Breach shall be reviewed by Research Governance Team and/or Quality Assurance and may be downgraded to a Non-Serious Breach, or a Deviation.

6.2 Recording & Reporting Deviations and Breaches

- Recording and reporting of deviations should use the following documents:
 - RAINdrop Log of Protocol Deviations, Breaches and Urgent Safety Measures
 - RAINdrop Breach Report Form
- All protocol deviations and breaches should be recorded in the Protocol Deviation and Breach Log as soon as a member of the research team is aware of them.
- The PI should be informed of all deviations and breaches and the PI should decide if the breach is potentially serious.
- If there is any uncertainty as to the significance or seriousness of the deviation/breach this should be discussed with the CI.

6.2.1 Protocol Deviations

- These should be recorded in the Protocol Deviation and Breach Log, there is no requirement for a report to be completed.
- All deviations should be recorded; this will allow any trends in deviations to be noted and action taken if necessary.
- The Research Nurse will email a copy of the Protocol Deviation and Breach Log to the RAINdrop Trial Coordinator at the end of each month.

6.2.2 Protocol Breaches

- Protocol breaches should be recorded in the Protocol Deviation and Breach Log and reported in the Protocol Breach Report
- The Protocol Breach Report should include a brief description of the breach, reason for the breach and any corrective and preventative actions already taken (Corrective Action and Preventative Action, CAPA).
- The Protocol Breach Report should be emailed to the CI and copied to the CTM.

- The Protocol Deviation Report will be reviewed and if further corrective and preventative actions are required these will be discussed between the site, research team and Sponsor (if applicable).

6.2.3 Serious Protocol Breaches

- If a breach is assessed to be potentially serious by the PI it should be reported to the CI within 24 hours. The CI will inform the Sponsor who will decide whether the breach should be reported to Sponsor. Potentially serious breaches should be recorded and reported as Protocol Breaches as above.

6.2.4 Contact Details

- Chief Investigator: phyo.myint@adbn.ac.uk
- Trial Manager: raindroptm@dundee.ac.uk
- RAINDroP trial coordinator: b.brikinns@abdn.ac.uk
- Sponsor: pharmaco@abdn.ac.uk [CI inform / reporting]

6.3 Protocol Deviations and Breaches Associated documents

- The latest versions of all documents can be found in the generic documents folder on the Staff Portal. Links to the TASC SOPs can be found in the SOP folder on the Staff Portal. These SOPs should not be printed out to ensure the most up-to-date versions are used.
 - Breach & Deviation Log
 - Breach Report.

7. Monitoring

7.1 Trial monitoring

Trial Monitoring will be carried out by the sponsor: University of Aberdeen. A Monitoring Plan will be provided where Monitoring is required.

Monitoring, where required, will be risk based and a combination of site visits and remote monitoring or remote monitoring only.

Separate to Sponsor Trial Monitoring TCTU will carry out remote data monitoring; this will require site to upload completed CRF pages, via LabKey.

7.2 Site visits

- Site initiation, provided by TCTU – prior to first patient first visit at each site.
- On-site / remote monitoring – as per Sponsor Monitoring Plan; depending on the number of patients recruited at site and performance of the site.

Additional on-site monitoring visits may be arranged if it is deemed necessary.

- Close out, provided by TCTU – after the last patient last visit at each site.
- See Monitoring Plan (where issued) a copy will be provided and filed in the ISF.

7.3 Centralised monitoring

Remote monitoring – will be scheduled at intervals to maintain oversight of sites. Higher recruiting sites will be asked to undertake remote monitoring visits more frequently.

The Sponsor monitor will contact the sites in order to complete Remote Monitoring.

If any minor issues are raised during the remote monitoring review, discussion with the site and the Clinical Trial Manager will take place to resolve these issues.

Any major issues resulting from this process may trigger a site monitoring visit.

Additional monitoring visits will be performed if required throughout the trial.

7.4 Documents to be monitored

Investigator Site File.

Informed Consent Forms – 100%.

Source document verification of critical data (endpoint data, iron treatment data / concomitant medications).

Source document verification of adverse event reporting (AE, SAE) – 100% of SAEs.

Source document verification of eligibility.

7.5 Trial Monitoring Associated documents

The latest versions of all documents will be found in the documents folder on the Staff Portal of the RAINDroP web site. Links to the University of Aberdeen and TASC SOPs will be found in the SOP folder on the Staff Portal / or via University of Aberdeen and TASC websites. These SOPs should not be printed out to ensure the most up-to-date versions are used.

8. Standard Operating Procedures and Working Practice Guidelines

8.1 SOPs

As a condition of co-sponsorship by University of Aberdeen and NHS Grampian all study sites will use the agreed RAINDrop SOPs and Policies.

All study sites will implement or be aware of the SOPs/Policies as detailed in the RAINDrop Agreed SOPs, or an appropriate local SOP approved by Sponsor. If your site has specific SOPs that mirror these mandatory topics please send a copy to the Study Trial Manager (email). They will be reviewed the University of Grampian Governance Manager and if approved, notification will be given to the local site to allow their implementation.

Please review the Sponsor agreed RAINDrop specific SOPs and establish (where applicable) that your site/personnel will be able to adhere to and implement. A Matrix of role specific SOP training is provided within Investigator Site File and via RAINDrop website. Once the PI and site personnel have reviewed the SOPs please sign/date the Study Specific SOP Sign-off Sheet (to be filed in the Investigator Site File). The web links will be used to access SOPs; SOPs should not be downloaded and filed. All current versions will be available via the University of Aberdeen and TASC websites (see Sponsor Agreed SOPs, Section 8.8.1 below) and via links provided on the RAINDrop Staff Portal www.raindrop.org.uk for reference.

- SOP updates will communicated by the RAINDrop trial coordinator.
 - The site staff will be required to complete and document reading for updated the SOP, using the Study Specific SOP Sign-off Sheet.

8.1.1 Sponsor agreed RAINDrop SOPs

Example provide below (please note the SOP list will be updated as per institutional SOP updates).

Standard OPERATING PROCEDURES			
UoA: https://www.abdn.ac.uk/clinicalresearchgovernance/sops/index.php			
TASC: http://www.ahspartnership.org.uk/tasc/for-researchers/sops			
SOP	TITLE	Version	SOP date
SOP QA 1	Management of SOPs	V3	01/04/2017
SOP-QA-2	Training Record	V3	01/06/2018
SOP QA 3	Protocol	V3	26/01/2018
SOP QA 4	Applying for Sponsorship	V3	01/04/2017
SOP QA 6	Study start up	V3	01/06/2018
SOP-QA-9	Receiving Informed Consent	V2	01/04/2017
SOP QA 10	Applying for Research Ethics Committee Opinion	V2	01/04/2017
SOP QA 13	Generation of Contracts	V3	01/04/2017
SOP QA 17	Project Committees	V4	01/06/2018
SOP QA 19	amendments	V3	01/04/2017
SOP QA 22	adverse Events	V3	01/06/2018
SOP-QA-23	Statistical analysis plans for clinical trials	V2	01/04/2017
SOP QA 25	deviations and breaches	V3	01/06/2018
SOP QA 27	good document practice	V2	01/04/2017
SOP-QA-28	Monitoring	V2	01/04/2017
SOP-QA-29	Audit	V2	01/04/2017
SOP-QA-31	Research project closure	V2	01/04/2017
SOP-QA-32	Archiving	V3	01/06/2018
SOP-QA-33	Research project publications and dissemination	V2	01/04/2017
SOP-QA-34	GCP Training	V4	01/06/2018
SOP-QA-36	Retention of Health Records of Clinical Trial Patients	V3	01/06/2018
SOP-QA-40	Multi-centred site selection	V2	01/06/2018
TASC SOP19	PREPARING AND MAINTAINING CASE REPORT FORMS (CRFs) FOR USE IN CLINICAL RESEARCH	7.0	11/10/2016
TASC SOP32	LOCKING CLINICAL STUDY DATABASES	4.0	15/03/2017
TASC SOP40	RANDOMISATION, BLINDING AND CODE BREAKING IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS	5.0	30-May-18
TASC SOP45	STANDARD OPERATING PROCEDURE FOR ESTABLISHING AND MAINTAINING A TRIAL MASTER FILE OR AN INVESTIGATOR SITE FILE IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS	5.0	12/07/2017
TASC SOP48	DATA MANAGEMENT IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS USING EXCEL	4.0	04-Feb-18
TASC SOP53	PROCEDURE FOR DATA MANAGEMENT SYSTEMS IN CLINICAL RESEARCH	1.0	20/06/2017
Study specific	Participant documents font and point size	1.0	18.04.2018
HIC Services	HIC services SOP 12 Recruitment Projects	2.0	01/01/2016